THE ASSESSMENT AND MODIFICATION OF CARDIOVASCULAR RISK IN INFLAMMATORY ARTHRITIS

by

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DECLARATION

The design of the non-steroidal withdrawal study was that of the myself and Professor Hilary Capell and Dr Rajan Madhok of the Centre for Rheumatic Diseases at Glasgow Royal Infirmary. Metrology was performed by myself (apart from one visit for a single patient when it was carried out by Sister Rosemary Hampson). Blood samples were processed by the routine haematology and biochemistry laboratories of Glasgow Royal Infirmary. Statistical analysis was carried out by myself and Ms Ann Tierney of the Centre for Rheumatic Diseases, Glasgow Royal Infirmary.

The design of the Mediterranean-type diet intervention study presented in this thesis originated from Professor Hilary Capell (Glasgow Royal Infirmary), Dr Anne McEntegart (Stobhill Hospital, Glasgow) and Dr Elaine Morrison (Southern General Hospital, Glasgow). All 3 study designers have given approval for my subsequent analysis and writing up of the results. Subsequent design and analysis of cardiovascular risk factors was that of myself and Professor Hilary Capell. Metrology was carried out in the 3 hospital sites by Sister Fiona McDonald (Glasgow Royal Infirmary), Sister Elizabeth McIvor (Stobhill Hospital, Glasgow) and Sister Audrey Rowan (Southern General Hospital, Glasgow). Dr Janet Scott and students from the Human Nutrition Department of the University of Glasgow carried out analysis of food frequency questionnaires. Blood samples were processed by the routine haematology and biochemistry laboratories of Glasgow Royal Infirmary, Stobhill Hospital and the Southern General Hospital. Statistical analysis was carried out by myself, Mrs Dorothy McKnight and Ms Ann Tierney (Centre for Rheumatic Diseases, Glasgow Royal Infirmary).

The relevant publishers have given their kind permission to allow inclusion of my published articles in this thesis.

I declare that this thesis has been composed by myself.

It has not been previously submitted for a higher degree.

Gayle Elspeth McKellar, October 2012

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Annals of the Rheumatic Diseases 2007; 66:1239-43

McKellar G, Hampson R, Tierney A, Capell HA, Madhok R.
"A feasibility study to assess the impact of non-steroidal anti-inflammatory drug withdrawal in patients with stable rheumatoid arthritis".
Journal of Rheumatology 2011; 38:2150-2

Review articles

McKellar G, Madhok R, Singh G.
"The problem with NSAIDs: what data to believe?"
Current Pain and Headache Reports 2007; 11:423-7

McKellar G, Madhok R, Singh G.
"Update on the use of analgesics versus non-steroidal anti-inflammatory drugs in rheumatic disorders: risks and benefits".
Current Opinion in Rheumatology 2008; 20:239-45

McKellar G, Singh G.
"Celecoxib in arthritis: relative risk management profile and implications for patients".
Therapeutics and Clinical Risk Management 2009; 5:889-96

McKellar GE, McCarey DW, Sattar N, McInnes IB.
"Role for TNF in atherosclerosis? Lessons from autoimmune disease".
Nature Reviews Cardiology 2009; 6:410-7

Editorials

Madhok R, Wu O, **McKellar G**, Singh G.
"Non-steroidal anti-inflammatory drugs – changes in prescribing may be warranted".
Rheumatology 2006; 45:1455-7

Book chapters

McKellar G, Singh G.
"Non-steroidal anti-inflammatory drugs and COX-2 inhibition".
Year in Rheumatic Diseases 2006
Clinical Publishing. ISBN 978-1-84692-018-9

PRESENTATIONS TO LEARNED SOCIETIES

Chapter 3 – A pilot study of non-steroidal anti-inflammatory drug withdrawal in patients with stable rheumatoid arthritis

1) McKellar G, Hampson R, Tierney A, Capell HA, Madhok R.
"A pilot study of non-steroidal withdrawal in patients with stable rheumatoid arthritis".
Oral presentation, SSR autumn meeting, Perth, November 2007
Reference: Scottish Medical Journal 2008; 53(3):49-51

2) McKellar G, Hampson R, Tierney A, Capell HA, Madhok R.
"The feasibility and acceptability of withdrawal of non-steroidal anti-inflammatory drugs from patients with stable rheumatoid arthritis".
Poster presentation, ACR scientific meeting, Boston, USA, November 2007
In *Proceedings of the ACR: Annual Scientific Meeting, 2007,* abstract no.968

3) McKellar G, Hampson R, Tierney A, Madhok R, Capell HA.
"The impact of non-steroidal withdrawal on blood pressure and disease activity score in patients with stable rheumatoid arthritis".
Poster presentation, EULAR annual meeting, Paris, France, June 2008
Reference: Annals of the Rheumatic Diseases 2008; 67 (Suppl II):306

4) McKellar G, Hampson R,Tierney A, Capell HA, Madhok R.
"The impact of non-steroidal withdrawal on blood pressure and disease activity score in patients with stable rheumatoid arthritis: a feasibility study".
Poster presentation, Royal College of Physicians and Surgeons of Glasgow Triennial Conference, Glasgow, November 2008
Reference: Scottish Medical Journal 2009; 54(1) (Suppl II):14

Chapter 4 – A pilot study of a Mediterranean-type diet intervention in female patients with rheumatoid arthritis

1) Scoular J, Morrison E, **McKellar G**, Hampson R, Mackle G, Tierney A, McEntegart A, Capell HA.
"Mediterranean diet intervention in rheumatoid arthritis – influence of deprivation and feedback from cookery courses".
Poster presentation, EULAR annual meeting, Vienna, Austria, June 2005
Reference: Annals of the Rheumatic Diseases 2005; 64 (Suppl III):190

2) McKellar G, Hampson R, Capell HA, Morrison E, McEntegart A, Tierney A, Mackle G, Macdonald R, Scott J, Scoular J.
"A pilot study of a Mediterranean diet in female patients with rheumatoid arthritis living in areas of social deprivation".
Poster presentation, BSR annual meeting, Glasgow, May 2006
Reference: Rheumatology 2006; 45 (Suppl 1):i1-i197

Chapter 5 – The influence of social deprivation on cardiovascular risk scores in female patients with rheumatoid arthritis

1) McKellar G, McEntegart A, Morrison E, Hampson R,Tierney A, Capell HA.
"The influence of social deprivation on cardiovascular risk factors in a cohort of female rheumatoid arthritis patients living in an inner city area: the value of the ASSIGN score in predicting ten-year risk".
Poster presentation, ACR scientific meeting, Boston, USA, November 2007
In *Proceedings of the ACR: Annual Scientific Meeting, 2007,* abstract no.999

2) McKellar G, Hampson R, Morrison E, McEntegart A, Capell HA.
"Comparison of three different scoring systems in predicting ten-year cardiovascular risk in female rheumatoid arthritis patients".
Concurrent oral presentation, BSR annual meeting, Liverpool, April 2008
Reference: Rheumatology 2008; 47(Suppl 2):ii1-ii198

RELEVANT FELLOWSHIPS AND PRIZES AWARDED

1) Ritchie Trust Fellowship, Royal College of Physicians and Surgeons of Glasgow, 2006

"A pilot study to establish the feasibility and acceptability of withdrawing non-steroidal anti-inflammatory drugs from patients with stable rheumatoid arthritis". Report available at:
http://www.rcpsg.ac.uk/FellowsandMembers/BenefitsandServices/AwardsandScholarships/Documents/G%20McKellar.pdf

2) Walker Trust Fellowship, Royal College of Physicians and Surgeons of Glasgow, 2007

"Strategies to assess cardiovascular risk in the rheumatic diseases".
Report available at:
http://www.rcpsg.ac.uk/FellowsandMembers/BenefitsandServices/AwardsandScholarships/Documents/Walker%20trust%20Report%20-%20G%20McKellar.pdf

3) First prize winner, oral presentation, Scottish Society for Rheumatology Autumn meeting, 2007

McKellar G, Hampson R, Tierney A, Capell HA, Madhok R.
"A pilot study of non-steroidal withdrawal in patients with stable rheumatoid arthritis".

4) Joint first prize winner of the Alexander Bryce Essay Prize, University of Glasgow Human Nutrition Department, 2008 (section: postgraduate doctors who were medical students of the University of Glasgow)

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5) EULAR travel bursary award winner for annual meeting, Paris, 2008

McKellar G, Hampson R, Tierney A, Madhok R, Capell HA.
"The impact of non-steroidal withdrawal on blood pressure and disease activity score in patients with stable rheumatoid arthritis".

6) Third prize winner, poster presentation. The Royal College of Physicians and Surgeons of Glasgow Triennial Conference, 2008

McKellar G, Hampson R, Tierney A, Capell HA, Madhok R.
"The impact of non-steroidal withdrawal on blood pressure and disease activity score in patients with stable rheumatoid arthritis: a feasibility study".

ABBREVIATIONS

ACPA	anti-citrullinated peptide antibody
ACR	American College of Rheumatology
AIx	augmentation index
APC	Adenomatous Polyp prevention with Celecoxib
APPROVe	Adenomatous Polyp Prevention On Vioxx
AS	ankylosing spondylitis
ASSIGN	Assessing cardiovascular risk using SIGN guidelines
BeST	Behandel Strategieën (Dutch acronym)
BHS	British Hypertension Society
BMI	body mass index
BP	blood pressure
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
CARRÉ	Cardiovascular research and rheumatoid arthritis (Dutch acronym)
CCF	congestive cardiac failure
CCL21	chemokine (C-C motif) ligand 21
CHD	coronary heart disease
CI	confidence interval
cIMT	carotid intima media thickness
CLASS	Celecoxib Long-term Arthritis Safety Study
CONDOR	Celecoxib versus Omeprazole and Diclofenac in patients with Osteoarthritis and Rheumatoid arthritis

CRESCENT	Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation Trial
CV	cardiovascular
CVD	cardiovascular disease
COX	cyclooxygenase
CRP	C-reactive protein
DART	Diet And Reinfarction Trial
DAS	disease activity score
DAS28	disease activity score – 28 joints
DAS44	disease activity score – 44 joints
DMARD	disease modifying anti-rheumatic drug(s)
E3N	Etude Epidémiologique auprès de femmes de l'Education Nationale
EDTA	ethylenediaminetetraacetic acid
ECAM	endothelial cell adhesion molecule
EDN1	endothelin-1 gene locus
eGFR	estimated glomerular filtration rate
EMS	early morning stiffness
EPIC	European Prospective Investigation into Cancer and nutrition
ESR	erythrocyte sedimentation rate
ET	endothelin
EULAR	European League Against Rheumatism
Fab	fragment antigen binding

FDA	Food and Drug Administration
FFQ	food frequency questionnaire
FMD	flow mediated dilation
FVL	fruit, vegetables and legumes
g	gram(s)
GFR	glomerular filtration rate
GH	global health
GI	gastrointestinal
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto miocardio
GP	general practitioner(s)
GWAS	genome wide association study / studies
HAQ	health assessment questionnaire
HDL	high-density lipoprotein
HLA	human leukocyte antigen
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HOMA-IR	homeostatic model assessment of insulin resistance
HOT	Hypertension Optimal Treatment
HR	hazard ratio
hsCRP	high-sensitivity CRP
IA	intra-articular
ICAM	intercellular cell adhesion molecule
IDL	intermediate-density lipoprotein

Ig	immunoglobulin
IHD	ischaemic heart disease
IL	interleukin
IL2RA	interleukin-2 receptor alpha chain
IM	intramuscular
INTERHEART	A study of risk factors for first myocardial infarction in 52 countries and over 27,000 subjects
JBSCRP	Joint British Societies Coronary Risk Prediction
JUPITER	Justification for the use of stating in Prevention: an Intervention Trial Evaluating Rosuvastatin
kg	kilogram(s)
l	litre(s)
LDL	low-density lipoprotein
LREC	local research ethics committee
LVSD	left ventricular systolic dysfunction
m	metre(s)
MCP	metacarpophalangeal
MCS	mental component summary (of SF12)
MDRD	modification of diet in renal disease
MEDAL	Mulitnational Etoricoxib and Diclofenac Arthritis Long-term
mg	milligram(s)
MHRA	Medicines and Healthcare Products Regulatory Authority
MI	myocardial infarction

ml	millilitre(s)
mm	millimetre(s)
mmHg	millimetre(s) of mercury
mmol	millimole(s)
MONICA	multinational Monitoring of trends and determinants in cardiovascular disease
MTP	metatarsophalangeal
NHS	National Health Service
NICE	National Institute for Clinical Excellence
nm	nanometre(s)
NSAID	non-steroidal anti-inflammatory drug(s)
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OA	osteoarthritis
OR	odds ratio
PCS	physical component summary (of SF12)
PG	prostaglandin
PIP	proximal interphalangeal
PreSAP	Prevention of colorectal Sporadic Adenomatous Polyps
PsA	psoriatic arthritis
PTPN22	protein tyrosine phosphatase non-receptor type 22
PWV	pulse wave velocity
RA	rheumatoid arthritis

RAI	Ritchie articular index
RF	rheumatoid factor
RR	relative risk
SCORE	Systemic Coronary Risk Evaluation
SDAG	Scottish Diet Action Group
SDAP	Scottish Diet Action Plan
SF12	short form 12-item survey
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple Deprivation
SMR	standardised mortality ratio
SNP	single-nucleotide polymorphism
SSR	Scottish Society for Rheumatology
SUCCESS	Successive Celecoxib Efficacy and Safety Study
TARA	Trial of Atorvastatin in Rheumatoid Arthritis
TC	total cholesterol
TGFB	transforming growth factor-beta
TH	T-helper cells
TNF	tumour necrosis factor
TRAF1/C5	tumour necrosis factor receptor-alpha factor 1 / complement component C5
UK	United Kingdom
UNESCO	United Nations Educational, Scientific and Cultural Organisation
USA	Unites States of America

VAS	visual analogue scale
VCAM	vascular cell adhesion molecule
VIGOR	Vioxx Gastrointestinal Outcomes Research
VLDL	very low-density lipoprotein
VTCN	V-set domain containing T-cell activation inhibitor
WHO	World Health Organization
WHR	waist: hip ratio
WMA	World Medical Association

SUMMARY

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that primarily affects synovial joints and is the commonest form of inflammatory polyarthritis. RA potentially confers significant morbidity, loss of function and reduced quality of life. It is a multisystem disorder with extra-articular manifestations affecting skin, cardiovascular, respiratory and haematological systems.

There is an associated premature mortality associated with RA which is mainly attributable to cardiovascular disease (CVD). Much has been published on the associated increased CVD risk which RA confers, which includes increased incidence of myocardial infarction, congestive cardiac failure and hypertension. Active RA is associated with a higher burden of both traditional cardiovascular (CV) risk factors (cigarette smoking, dyslipidaemia and hypertension) and novel risk factors (endothelial dysfunction, arterial stiffness and insulin sensitivity) than would be expected in the general population. Furthermore, chronic inflammation may be atherogenic. Certain drug therapies may contribute to CV risk, such as steroids and anti-inflammatories. Whereas other drug therapies, such as anti-tumour necrosis factor agents, may modulate CV risk.

There have been many recent controversies regarding anti-inflammatories, both non-selective non-steroidal anti-inflammatory drugs (NSAID) and cyclooxygenase2 (COX2) inhibitors. These include gastrointestinal system side-effects, renal dysfunction and hypertension. The most publicised of these issues was the withdrawal of rofecoxib in 2004 by its manufacturers after clinical trial data emerged which showed a 3.5% incidence of myocardial infarction or ischaemic stroke in patients with no pre-existing CVD who were receiving therapy. This lead to a scrupulous review in the medical journals of the relative CV risks of both NSAID and COX2 inhibitor groups as whole; as well as sub-analysis and comparison of individual preparations. In 2006 the American Heart Association recommended that in order to minimise CV risk, any patient prescribed an anti-inflammatory should have the lowest dose administered for the shortest possible time.

Furthermore, it is clear from the literature that it is not just underlying disease processes and medication that can impact on CV risk. Dietary modification can have a large bearing on health outcomes. Large epidemiological studies from Greece and other countries of southern Europe have confirmed that adherence to a Mediterranean-type diet is associated with increased longevity and reduced CVD. A Mediterranean-type diet is typically rich in olive oil, fruit, vegetables, legumes and fish, with a low intake of red-meat. This type of diet is often complemented by a modest amount of alcohol, usually red wine, taken alongside meals. This contrasts starkly with the typical diet of the west of Scotland – 'famed' for its high amount of saturated fat and sugar and relatively low consumption of fruit and vegetables.

Of late, much interest has been generated regarding the potential relationship between social deprivation and effect on health in general, particularly: diet, cardiovascular disease and RA outcomes. This is of particular relevance to Glasgow which has some of the most deprived areas in Scotland. While traditional CV risk assessment calculators have focussed on traditional markers such as blood pressure and cholesterol, newer validated scores include a score of deprivation, higher areas of social deprivation are associated with higher incidence of CVD, and family history of CVD.

Aims

In this thesis my aims were to explore the effect of novel interventions on various aspects of RA, predominately to assess CV risk further and review whether certain aspects of risk could be modified.

First of all, I investigated the feasibility and effect of anti-inflammatory withdrawal in patients with well-controlled RA (that is to say, patients with mild disease activity scores). The rationale to the NSAID withdrawal study was that removal of therapy plus any required active intervention would provide equivalent symptom control to that achieved by continuing NSAID. Other prescribed RA therapies were continued. The impact of this intervention was assessed by disease activity score, pain score and functional assessments. Secondary study outcomes included the effect of drug withdrawal on blood pressure control, gastrointestinal symptoms and renal function.

Subsequently, the impact of a Mediterranean-type diet on disease activity within the Glasgow RA population was reviewed. The study was set up to assess if existing resources could be used as much as possible and replicate a Mediterranean-type diet in a real-life setting, predominately in areas of social deprivation in the east end and south side of Glasgow. Feasibility and acceptability to participants was explored. Additionally, the impact of such a dietary intervention on disease activity, CV parameters and haematological markers was assessed.

Finally, given recent evidence linking social deprivation with CV risk as well as poor RA outcomes, an analysis was undertaken using the cohort recruited to the Mediterranean-type diet. Results of CVD risk calculations according to conventional and new algorithms were compared.

Results

Thirty patients with RA and a 44-joint disease activity score of ≤2.8 were recruited to a 12-week anti-inflammatory withdrawal study. All completed the study period without requiring re-introduction of anti-inflammatories and all continued on their previously prescribed RA therapy. Eleven patients required a steroid injection at either the 6 or 12-week study visit and only 1 required escalation of disease modifying therapy. There was no significant deterioration in disease activity score or components at the 12-week assessment. A significant improvement in blood pressure was recorded with a maximal median reduction of 7 millimetres of mercury (p=0.037**).**

Seventy-five patients with RA were recruited to the intervention arm of the Mediterranean-type dietary study and attended weekly cookery classes over a 6 week period. Fifty-five patients with RA were recruited to the control arm and received basic printed information only. All routine medication was continued and patients assessed at baseline, 3 and 6 months. Significant benefits were seen in the intervention group with regards to features of RA activity: reduced duration of early morning stiffness at 6 months (p=0.041), patient global health assessment score at 6 months (p=0.002) and pain score at 3 and 6 months (p= 0.011 and 0.049 respectively). Then intervention group demonstrated a benefit in systolic blood

pressure. There was a significant increase in fruit, vegetable and legume consumption as assessed by food frequency questionnaire.

The substantial amount of baseline demographic and CV data collected from the Mediterranean-type diet study allowed a comprehensive assessment of the influence of social deprivation on CV risk scores in a cohort of female patients with RA living in the Glasgow area to be undertaken. Three different CV risk calculators were used: Joint British Societies Coronary Risk Prediction, Framingham and the newer, Scottish, ASSIGN score which incorporates social deprivation. ASSIGN was more likely to classify an individual with a >20% 10-year CVD risk (23% of total cohort) than Framingham or JBSCRP. By using ASSIGN, an additional 16 individuals were identified as having a >20% 10-year CV risk than would have been identified by using traditional JBSCRP alone.

Conclusions

The anti-inflammatory withdrawal intervention was limited by an open-label design and small participant numbers (n=30). However, it was well tolerated and did not result in the need for significant medical intervention, nor loss of disease control. A significant improvement in systolic blood pressure was noted over the study follow-up. To my knowledge this is the first supportive evidence to guide the limitation of anti-inflammatory use in patients with stable RA and should inform further work in this area.

The Mediterranean-type diet intervention demonstrated that a 6-week intervention can prove instrumental in increasing intake of healthy foods at a relatively low cost. This dietary intervention was well received, on reviewing feedback, and resulted in beneficial effects on RA disease features as well as on blood pressure. This could be an area of future disease modification which is cost-effective and easy to implement as well as being popular with patients.

Using the ASSIGN score allowed the identification of a greater number of study participants with a high 10-year CVD risk score. This is in addition to the increased CV risk which RA confers. Increased use of this score would allow the targeting of a greater number of patients to target interventions and minimise future CVD.

CHAPTER 1

Introduction

1.1 RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory multi-system disorder that primarily affects synovial joints and is the commonest form of inflammatory polyarthritis. The condition was first described as a distinct disease entity in the 19th century (1) and the term 'rheumatoid arthritis' was first used by Alfred Baring Garrod in 1859 (2). RA potentially confers significant morbidity, loss of function and reduced quality of life. There is an associated premature mortality mainly attributable to cardiovascular disease (CVD). Active RA is associated with a higher burden of both traditional cardiovascular (CV) risk factors (cigarette smoking, dyslipidaemia and hypertension) and novel risk factors (endothelial dysfunction and insulin resistance) than would be expected in the general population. Furthermore, chronic inflammation may be atherogenic and certain drug therapies may contribute to or modulate CV risk.

1.1.1 Clinical features

RA is a symmetrical inflammatory polyarthritis which affects both large and small synovial joints. It manifests as pain, stiffness and swelling of these joints with subsequent erosive destruction of surrounding articular cartilage and bone. The onset of RA may occur at any stage of adult life but the most frequent time is during middle age; the peak occurrence in females is around the time of the menopause. Females are 3-4 times more likely to be affected than males. RA affects approximately 1% of the worldwide population (3) and has a minimum prevalence of 1.16% in United Kingdom (UK) females and 0.44% in UK males (4).

In the majority of cases, RA displays a chronic course of progressive inflammation with periods of disease flare and quiescence. Early morning stiffness (EMS) may precede awareness of pain and swelling. The most commonly affected areas are the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints in the hands, wrist joints and the metatarsophalangeal (MTP) joints in the feet. Unlike in osteoarthritis (OA) and psoriatic arthritis (PsA), the distal interphalangeal joints are not affected. Although primarily affecting joints, RA is associated with extra-articular disease which can manifest in any of the body's organs.

1.1.2 Serological features

RA can be sub-divided into the presence or absence of rheumatoid factor (RF). RF is associated with more aggressive and erosive disease, with increased incidence of extra-articular manifestations. The use of anti-citrullinated protein antibody (ACPA) has become established in the diagnosis of RA more recently, with a higher specificity but lower sensitivity than RF (5).

1.1.3 Diagnosis

RA is diagnosed by history, objective evidence of joint swelling and tenderness, immunology profile, elevated inflammatory markers and potentially by confirmation of radiological damage. The initial 1988 American College of Rheumatology (ACR) diagnostic criteria (6) have been superseded by the joint ACR and European League Against Rheumatism (EULAR) guidelines of 2010 in an attempt to facilitate earlier detection of those with inflammatory arthritis who would benefit from intervention (7).The diagnosis is aimed at the classification of newly presenting patients. The diagnostic criteria are summarised in Table 1.1; at least 1 joint with definite clinical synovitis is required and this swelling should not be better explained by another condition. The new criteria have been validated in clinical practice with good results (8) (9).

Table 1.1 – 2010 ACR/EULAR diagnostic criteria for rheumatoid arthritis

CRITERIA	SCORE
JOINT INVOLVEMENT	
1 large joint	0
2-10 large joints	1
1-3 small joints (± large joints)	2
4-10 small joints (± large joints)	3
>10 joints (at least 1 small joint)	5
SEROLOGY	
Negative RF *and* negative ACPA	0
Low positive RF *or* low positive ACPA	2
High positive RF *or* low positive ACPA	3
ACUTE PHASE REACTANTS	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
DURATION OF SYMPTOMS	
<6 weeks	0
≥6 weeks	1

A score of ≥6/10 is required for a definite diagnosis of RA

Adapted from (7)

1.1.4 Treatment

The treatment of RA has changed dramatically in the last 3 decades. Initially, the focus was simply on improving symptoms by the use of analgesics and anti-inflammatories. Currently, these therapies are likely to have been self-prescribed by the individual or recommended by the general practitioner (GP) before specialist rheumatology review occurs.

Steroids have long been successfully employed by oral, intra-articular (IA) or intramuscular (IM) routes to reduce inflammation; while they are not able to be purchased over-the counter by the individual, they continue to be prescribed by GPs and rheumatologists. Low dose oral glucocorticoids given in addition to standard therapy in RA can reduce the rate of erosion progression, especially in those with a disease duration of less than 2 years (10). The adverse effects of low dose prednisolone are modest – the immediate concern of loss of bone mineral density can be addressed early on. Concerns do persist, however, regarding longer term adverse effects of continued glucocorticoids use, such as increased CV risk via hypertension (11).

1.1.4.1 Disease modifying anti-rheumatic drugs

The main class of drug demonstrated to improve symptoms and prevent damage and disability is the disease modifying anti-rheumatic drugs (DMARD). Commonly prescribed DMARD in the UK include: methotrexate (the most frequently used and so-called "anchor drug"), sulfasalazine, hydroxychloroquine, leflunomide and sodium aurothiomalate. They are instigated as soon as possible after the time of diagnosis. Combinations of DMARD are now increasingly used to gain tight control of RA disease activity (12) (13) with the aim of achieving "remission" of disease activity, as described in more detail in Section 1.1.7.

1.1.4.2 Biological therapy

The advent of tumour necrosis factor (TNF) inhibitors have revolutionised RA therapy still further. TNF and TNF inhibitors are discussed in more detail in Section 1.2.2 and 1.2.2.1. Adalimumab, etanercept and infliximab are licenced for use after failure of 2 or more DMARD (one which must be methotrexate) when a patient

has active RA as manifest by a 28-joint disease activity score (DAS28) of >5.1 on 2 separate occasions greater than 1 month apart. Ideally, these drugs are co-prescribed with methotrexate but can be given alone (14). Rituximab, an anti B-lymphocyte CD20 biological therapy, is now licenced for use in RA after failure of a TNF inhibitor; also ideally co-prescribed with methotrexate (15).

1.1.5 The role of the multi-disciplinary team

The multi-disciplinary team is of vital importance in the care of a patient with RA. The team members include nurse specialists, physiotherapists, occupational therapists and podiatrists. A shared-care arrangement between hospital and primary care physicians is crucial to the safe administration of drugs and follow-up of patients. Orthopaedic surgeons have a role in managing patients with significantly damaged joints in whom surgical intervention in the only remaining option.

1.1.6 Outcome measures

Outcome measures can be used to assess the efficacy of new treatments and to help target increasingly expensive therapies towards those with the greatest need and potential benefit. The ACR response criteria assesses improvement in swollen joints, tender joints, pain, disability, inflammatory markers and patient and physician global health (GH) scores (16). Other response criteria and outcome measures include the traditional or 44-joint disease activity score (DAS or DAS44) and DAS28 which are detailed in Section 2.4. Table 1.2, below, describes how any improvement in DAS28 from “baseline” to “endpoint” can be used to grade outcome.

Table 1.2 – Using change in DAS28 to determine outcome

DAS28 at endpoint	Improvement in DAS28 from baseline		
	>1.2	**>0.6 and <1.2**	**<0.6**
<3.2	Good	Moderate	None
3.2-5.1	Moderate	Moderate	None
>5.1	Moderate	Moderate	None

Adapted from (17)

1.1.7 Remission

Clinical remission in RA is a concept which has been developed over the last 30 years since the publication of ACR criteria in 1981 (18). It was determined by the presence of at least 5 out of 6 criteria on 2 consecutive months: minimal early morning stiffness, low erythrocyte sedimentation rate (ESR), no fatigue and the absence of painful, tender or swollen joints. Basing remission on disease activity was developed further in the 1990s with a DAS44 of <1.6 or a DAS28 of <2.6 being criteria for remission (described further in Table 2.5) (17, 19) (20) (21) . More recently, the ACR have published definitions of remission to be used in clinical trials based on tender and swollen joint counts, C-reactive protein (CRP) and patient or physician GH assessments (22).

1.2 PATHOGENESIS OF RHEUMATOID ARTHRITIS

The onset of arthritis is preceded by a "pre-articular" period of autoimmunity where immunoglobulin (Ig) as RF or ACPA is present (23) (24). During this time, lipid dysregulation can occur, leading to the earliest initiation of CV co-morbidity (25). Subclinical synovitis may be present at this stage and clinically evident disease will follow thereafter. The triggers that lead to autoimmunity are not fully known. Genetic factors may account for approximately 30% of the risk of

developing RA. Environmental factors (e.g. known and unknown micro-organisms, smoking, mechanical stress) also play a key role.

The synovial lining of a joint provides nutrients to the avascular cartilage as well as producing lubricants such as hyaluronic acid. In RA the synovial lining becomes thickened with an inflammatory infiltrate which includes B cells, T cells, neutrophils and macrophages. T cell infiltrates are prominent in RA synovium (26). The role of B cell pathology in RA is becoming clearer with clinical studies establishing the role for CD20 targeting, such as with rituximab (27) (28). Discovering the role of TNF has revolutionised thinking on the pathogenesis and treatment of RA, and this is described in more detail in Section 1.2.2.

1.2.1 Genetics

The major susceptibility genes identified for RA, as well as for inflammatory polyarthritis, in Northern Europeans are human leukocyte antigen (HLA)-DRB1 (29) and protein tyrosine phosphatase non-receptor type 22 (PTPN22), estimated to account for approximately 40% of total genetic risk for RA (30) (31). The majority of patients with RA carry the HLA-DRB1 allele. The shared epitope is a 5 amino acid sequence motif (32), the presence of which is associated with certain RA outcomes such as erosive disease and disability as well as the presence of RF and ACPA.

The advent of the Human Genome Project allowed genome wide association studies (GWAS) to become the most powerful and extensively used approach in discovering susceptibility variants for complex disease processes, such as RA. GWAS has resulted in over 30 genetic loci being confidently associated with RA predisposition, with thousands of single-nucleotide polymorphisms (SNP) explaining an additional 20% of disease risk (in addition to HLA-DRB1 and PTPN22) (33). These include: V-set domain-containing T-cell activation inhibitor 1 (VTCN1) polymorphisms – which play a pivotal role in regulating the immune system (34), common variants at CD40 gene locus (35), interleukin (IL)-2 receptor alpha chain (IL2RA) (36), chemokine (C-C motif) ligand 21 (CCL21) (35) (36) and TNF receptor alpha factor 1/complement component C5 (TRAF1/C5) locus on chromosome 9 – relevant to chronic inflammation (37). It is thought that different mechanisms may be involved in the development of ACPA-positive versus ACPA-negative RA (far fewer genetic risk

factors are associated with the latter). The genetics of RA in relation to CVD is discussed in more detail in Section 1.5.7.

1.2.2 Tumour necrosis factor

Arguably the greatest single advance in the management of RA has been the identification of the key role of the group of cytokines, TNF, in its pathogenesis. A multitude of pro-inflammatory and anti-inflammatory mediators have been characterized in the rheumatoid synovium, but among these, TNF, as identified in 1985 (38), seems to be pivotal. TNF is localised in the lining layer of the synovium and at the cartilage pannus junction.

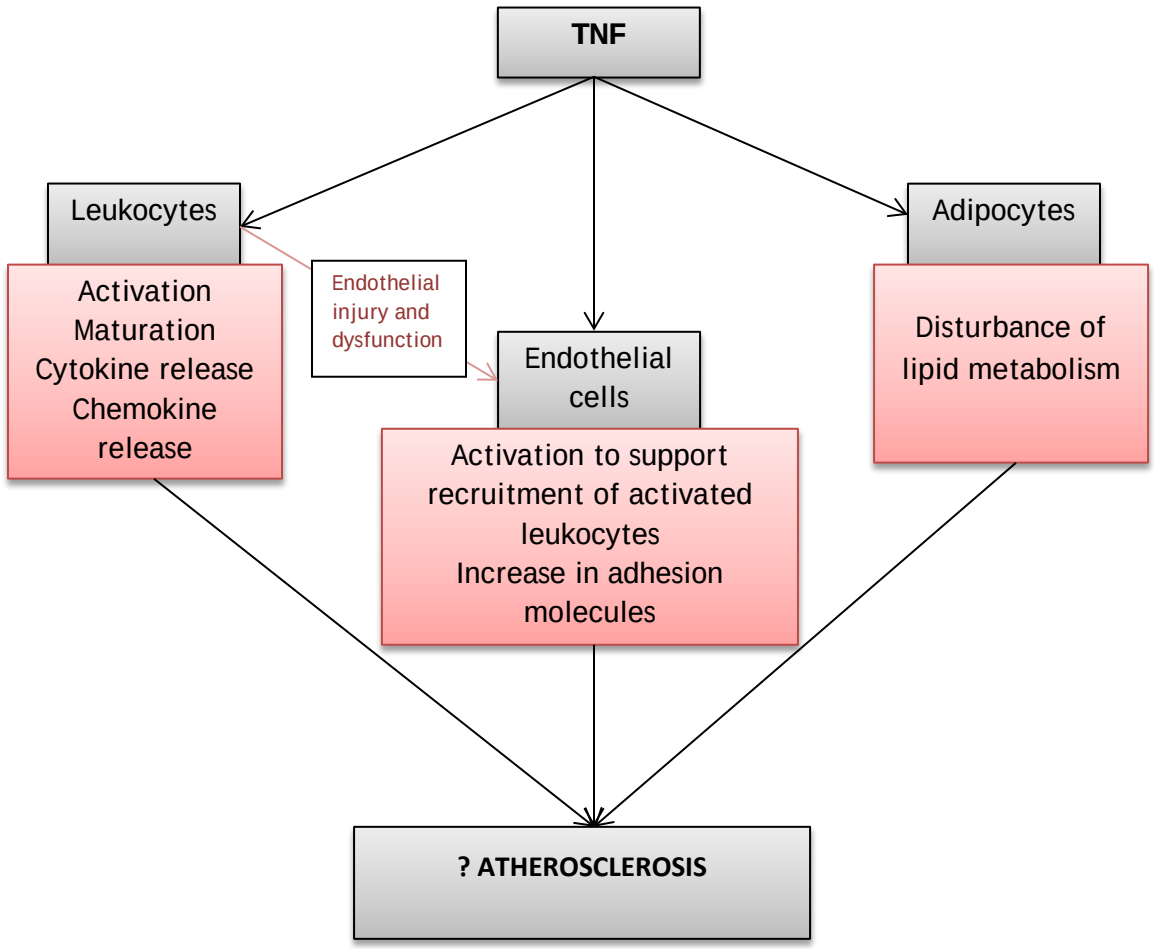
In vitro administration of neutralising anti-TNF antibody to primary RA synovial cultures results in a marked reduction in local cytokine production (39). Transgenic mice that express human TNF develop an inflammatory arthritis reminiscent of RA. Moreover, administration of anti-TNF antibody to transgenic mice with collagen-induced arthritis (40) resulted in a substantial reduction in inflammation and damage (41). This work led to the first human trials of infliximab for the treatment of RA, a chimeric monoclonal antibody which targets TNF; these studies demonstrated significant clinical benefit (42).

TNF-alpha (α) is a homotrimeric cytokine that can influence a variety of molecular and cellular events that contribute to several disease states including RA (43). It is produced by many cells including macrophages, T cells and B cells; its roles include regulation of leukocyte activation and maturation as well as cytokine and chemokine release as illustrated in Figure 1.1. As such, it is a central regulator of inflammatory cascades during both initiation and amplification of inflammatory reactions; via the induction of IL-6 release it acts as a critical regulator of the acute phase response. TNF-beta (β) is also known as lymphotoxin. A large number of other cytokines in the TNF family have been discovered and their key uses identified. Throughout the rest of this work, whenever the terms “TNF” or “anti-TNF” are used, TNF-α is specifically being referred to.

As outlined in Figure 1.1, TNF is thought to promote the inflammatory cascade within the arterial wall during development of atherosclerosis, in part by promoting

endothelial cell injury (44), a topic which will be explored in more detail later in this work. It may directly promote endothelial cell apoptosis and suppress the activities of endothelial cell progenitors that could sustain endothelial repair (45). TNF has also been implicated in promoting endothelial injury through recruitment of immune cells, such as neutrophils, which can mediate tissue destruction (46). Through adipocytes, TNF might contribute to the regulation of lipid and glucose metabolism (47) (48) which has direct clinical implications in the acute setting (for the necessary responses to injury or severe infection) and in the chronic setting (increased vascular risk). As such, TNF is considered a pleiotropic inflammatory cytokine with a central role in many pathophysiologic states and in associated comorbidities that affect more than just the primary target tissue.

Figure 1.1 – Actions of TNF and potential role in atherosclerosis



Adapted from (49)

1.2.2.1 TNF inhibitors

Until recently, only 3 TNF inhibitors (so-called anti-TNF drugs) were licensed for the treatment of RA: infliximab and adalimumab (both fully humanised monoclonal antibodies) and etanercept (a fusion protein of human soluble TNF receptor and the Fc component of human IgG1). All three of these biologic agents have been shown to be successful in controlling disease activity, improving physical function and attenuating radiological progression in RA (50) (51) (52). Additionally, a number of studies have described the effects of these agents on vascular risk surrogates and rates of vascular disease. Recently, golimumab (a fully humanised monoclonal antibody) and certolizumab (a PEGylated fragment antigen binding (Fab) fragment) have been added to the list of available TNF inhibitors.

In combination with methotrexate, a 20% reduction in clinical signs and symptoms is achieved in up to 70% of patients with RA receiving anti-TNF therapy. This improvement is often accompanied by slowing of joint destruction, as seen on plain radiographs (53).

Side-effects of anti-TNF include increased risk of infection, reactivation of tuberculosis, as well as the possibility of developing psoriasis, demyelination or paradoxical autoimmune features (53). Concerns were initially raised regarding increased incidence of malignancy with the use of these drugs. However, no overall conclusive evidence exists for an increased risk of solid tumours or lymphoproliferative disease above that which would be expected for the rest of the RA population (54).There is the increased risk of skin cancers (both malignant melanomas and non-melanotic skin cancers) with anti-TNF use; skin surveillance and preventative skin care is recommended. Overall vigilance is advised and caution should be exercised in prescribing anti-TNF therapy in patients with a previous malignancy or a pre-malignant condition.

1.3 CO-MORBIDITY IN RHEUMATOID ARTHRITIS

A co-morbid condition is a medical disorder which coexists along with the disease of interest. It may represent an active, past or transient illness and might be linked to the primary condition or its treatment, or be completely independent. Co-morbidities may greatly affect patients' quality of life, prognosis of condition and effectiveness of its treatment. Common co-morbidities in RA include anaemia, cerebrovascular disease, CVD, depression, gastrointestinal (GI) ulceration, infection, lymphoma, malignancy, osteoporosis and pulmonary disease. These may be atypical in presentation leading to difficulties and delays in identification (3). From the American National Data Bank for Rheumatic Diseases it has been extrapolated that a typical patient with RA has 1.3 co-morbidities (55). RA is associated with a higher prevalence of hypothyroidism and such patients have an increased risk of CVD and metabolic syndrome compared with their euthyroid RA counterparts (56) (57).

1.3.1 Early mortality

Survival amongst those with RA is significantly poorer than those without the condition. Unfortunately, RA mortality has not improved over the last few decades (58). A widening mortality gap has developed between those with RA and the general population. This is largely because RA mortality has remained unchanged while the general population's has improved with time (59).

1.3.2 Increased cardiovascular risk

The prevalence of CV traditional risk factors in patients with RA compared to controls has been well defined. Male gender, smoking, personal or family history of ischaemic heart disease (IHD), hypertension, hyperlipidaemia and diabetes, while important, have less of an impact on CVD in RA patients compared with non-RA counterparts (59). The incidence of CVD and associated death is similar to that of a diabetic population (60) (61). The presence of severe extra-articular manifestations of RA (including vasculitis, pericarditis, pleuritis, Felty's syndrome, scleritis, poly- and mononeuropathy) is associated with a significantly increased risk of first ever CVD event ($p<0.001$). When controlled for age, sex, smoking, RF and erosive

disease the association remained significant: hazard ratio (HR) 3.25, 95% confidence interval (CI) 1.59-6.64 (62).

The prevalence of CVD was determined in nearly 400 RA patients comprising the Dutch Cardiovascular Research and Rheumatoid arthritis (CARRÉ) study and compared with individuals from the Hoorn study (both diabetic and non-diabetic). After adjustment for conventional CV risk factors the odds ratio (OR) for CVD in individuals with type 2 diabetes was 2.0 (95% CI 0.9-4.5), and OR for those with RA was 2.7 (95% CI 1.2-5.9). The extent of the prevalence of CVD in RA patients is at least comparable to those with diabetes and as such has major implications for primary CV prevention strategies in RA (61) (63).

Increased CV risk in RA shall be explored in more detail in Sections 1.4 – 1.6 where different CV disease pathologies and their prevalence in RA will be discussed, possible mechanisms analysed and assessment and potential modification of CV risk assessment discussed. This will then lead into the presented information on anti-inflammatory drug use and associated CV risk in Section 1.7. Thereafter, the potential role of dietary modification such as with a Mediterranean-type diet in minimising CVD risk will be outlined in Section 1.8.

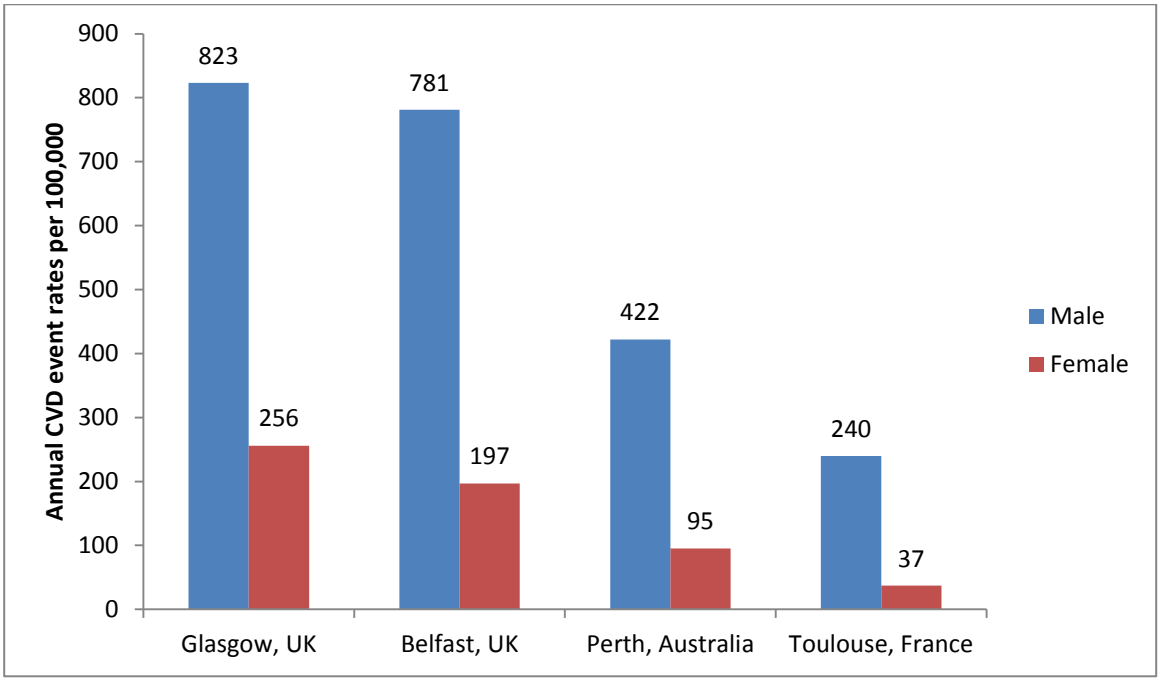
1.4 CARDIOVASCULAR DISEASE – CLINICAL ASPECTS

CVD is the main cause of death in the UK, attributable to 1 in 3 deaths. In the period 2001-2003, death rates from all CVD were greatest in the lowest socioeconomic group and lowest in the highest socioeconomic group. It is much more difficult to document CVD morbidity than mortality. Prevalence of CVD in the National Health Service (NHS) region of Greater Glasgow and Clyde in the period 2008-2009 was 4.4%, 2% for stroke and 12.5% for hypertension: and these rates are broadly similar to those seen throughout Scotland. Lifestyle contributes significantly to the high prevalence of CVD in the UK. For instance, 24% of the population of Scotland and Northern Ireland and 21% of the population of England and Wales were classified as smokers. In addition, the recommended amount of salt intake per day is 6 grams (g). Scottish figures of 2005 document an average

daily intake of 10.6g in men and 7.6g per day in women. In the same survey, only 37% of men and 33% of women reported a fruit and vegetable intake of 5 or more portions per day (64).

The World Health Organisation (WHO) Multinational Monitoring of Trends and Determinants of Cardiovascular Disease (MONICA) project was a 10-year study established in the 1980s to measure the trends in CV mortality, coronary heart disease (CHD) and cerebrovascular disease morbidity and to assess the extent to which these trends were related to changes in known risk factors, daily living habits, health care and major socioeconomic features measured at the same time in defined communities in different countries (65). Men and women aged 35 to 64 years were studied in 38 populations from 21 countries. As illustrated in Figure 1.2, Glasgow had the second highest male annual event rate (second only to North Karelia in Finland at 915 per 100,000) and the highest female annual event rate of all 38 of the populations worldwide which were studied.

Figure 1.2 – Age-standardised annual cardiovascular disease event rates per 100,000 population Event rates as defined by: sum of fatal+definite, fatal+possible, fatal+unclear, non-fatal+definite

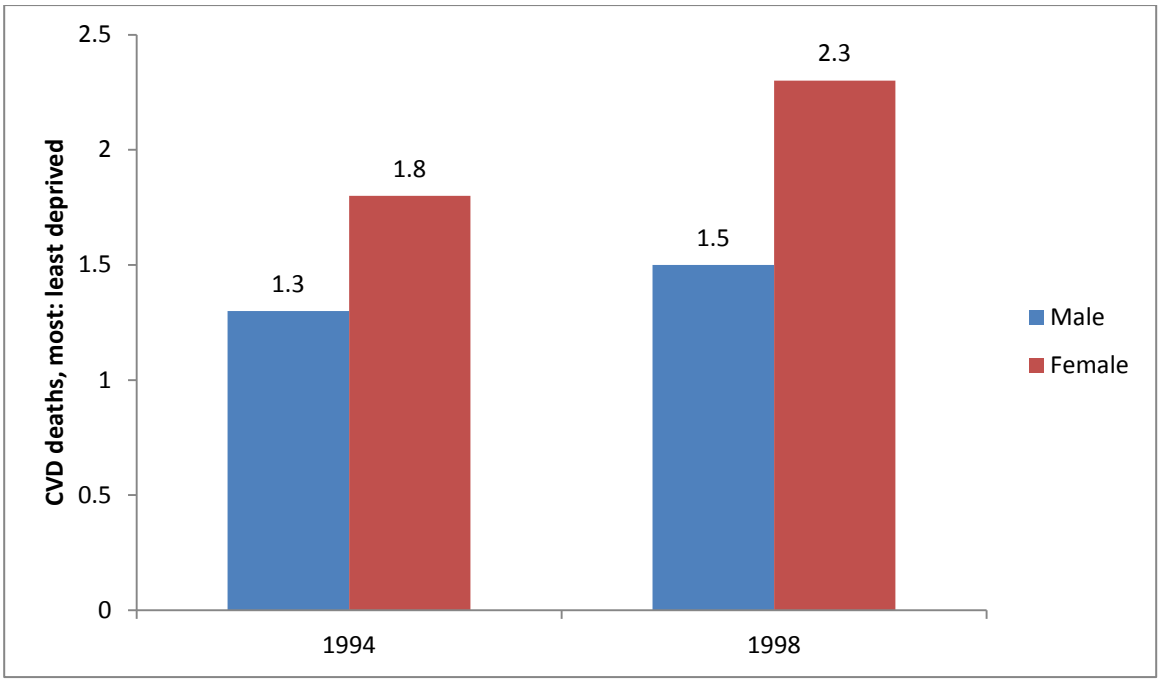


Adapted from (65)

1.4.1 Ischaemic heart disease

In the UK, deaths from CHD are highest in Scotland and the north of England and lowest in the south of England. In 2008, CHD caused 13% of all male and 9% of all female premature deaths (i.e. in those under 75 years old). In the under 75s, those living in the district of Glasgow City Council had the highest standardised death rate due to CHD both in Scotland and the entire UK occurring in 128.96 per 100,000 males and 45.61 per 100,000 females. While death rates from CHD are falling overall, there is no narrowing of the relative difference between the most and the least deprived, as described in Figure 1.3. The incidence of myocardial infarction (MI) in the period 2005-2007 was 20-35% higher in Scotland than in England. Case fatality rates were also higher in Scotland: 12% of males and 9% of females died (64).

Figure 1.3 – Ratio of cardiovascular disease deaths in Glasgow, most deprived compared with least deprived areas



Adapted from (64)

Yusuf's "Study of risk factors for first MI in 52 countries and over 27,000 subjects" is also known as the INTERHEART study. It identified that the following were potentially modifiable risk factors associated with MI: abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors (work, home, finance, depression and low self-efficacy), fruit and vegetable intake, consumption of alcohol and regular physical activity (66).

1.4.1.1 Ischaemic heart disease in patients with rheumatoid arthritis

It is recognised that patients with RA have an excess CV morbidity and mortality (67). Van Doornum's group studied almost 30,000 Australian patients who had a first CV event (either MI or stroke) over a 2-year period. Of the total group, 1.2% had RA. A higher case fatality rate was demonstrated in the RA group compared with non-RA patients, with an adjusted OR for CV death at 30 days of 1.9 (95% CI 1.3-2.7) (68).

In a retrospective medical chart review, 90 patients with RA admitted with an MI over a 10-year period were identified and compared with 90 age and gender matched controls (69). It was found that the RA patients were significantly less likely to receive acute coronary artery reperfusion therapy compared with controls: 16% versus 37% (OR 0.27, 95% CI 0.10-0.64). Additionally, these RA patients were also less likely to receive lipid-lowering therapy (40% versus 70%, OR 0.21, 95% CI 0.09-0.46) and beta-blockers (71% versus 83%, OR 0.42, 95% CI 0.18-0.96). These differences may contribute to the higher fatality rates of RA patients post-MI.

Electron-beam computed tomography can be used to establish the extent of coronary artery calcification by the calculation of calcium scores. A study of 227 patients showed higher calcium scores in patients with established RA compared with early disease and controls (p=0.001) (70). Coronary artery calcification was noted in 60.6% of patients with established RA (compared with 42.9% of those with early disease and 38.4% of controls, p=0.016). Smoking (OR 1.02, p=0.04) and elevated ESR (OR 1.02, p=0.05) were associated with more extensive coronary artery calcification, after adjustment for age and sex.

In addition, a systematic review and meta-analysis to assess CV mortality in an RA cohort was published in 2009 by Meune and colleagues (71). 17 studies, involving over 91,000 patients, were analysed. The overall pooled standardised mortality ratio (SMR) was 1.61 (95% CI 1.48-1.75, p<0.0001) corresponding to a 60% increase in risk of CV death in RA patients compared to the general population.

Maradit Kremers and colleagues have performed a number of epidemiological population-based cohort studies on the topic of inflammatory arthritis and CV risk. One of her team's studies assessed absolute CV risk in RA patients; this was found to be similar to patients without RA aged 5-10 years older, with increasing risk documented for the presence of additional CV risk factors, Table 1.3 (72). The presence of low BMI resulting in an even higher CV risk echoes the findings of this authors previous work (73). They have demonstrated an increased risk of CV death associated with markers of disease activity and extra-articular manifestations, even after correction for co-morbidities and traditional CV risk factors, Table 1.4 (74). Additionally, the group compared 603 RA patients with matched non-RA patients and identified increased risk of MI with subsequent hospitalisation as well as "silent" MI in the RA group, Table 1.5. The cumulative incidence of sudden death after 30 years of follow-up, after adjustment, was 6.7% in RA group and 3.8% in non-RA group (p=0.052). RA was associated with a higher cumulative incidence of "silent" MI (6%), after 30 years of follow-up than the non-RA group (3.7%), p=0.05. The prevalence of angina after 30 years of follow-up was 9.5% in the RA group and 14% in the non-RA group (75).

The potential mechanisms for such an association are detailed in Section 1.4.11.

Table 1.3 – Summary of Maradit Kremer et al's work: 10-year absolute cardiovascular risk in RA patients

Risk factor	Absolute 10-year risk
Aged 60-69 years, no other risk factors	16.8%
Plus smoking / diabetes / hyperlipidaemia / high BMI	60.4%
Plus low BMI	86.2%

Adapted from (72)

Table 1.4 – Summary of Maradit Kremer et al's work: Factors associated with risk of CV death in RA

Associated risk factor	Hazard ratio (95% confidence interval)
ESR >60 mm/hour	2.03 (1.45-2.83)
RA-associated lung disease	2.32 (1.11-4.84)
Vasculitis	2.41 (1.00-5.81)

Adapted from (74)

Table 1.5 – Summary of Maradit Kremer et al's work: Risk of myocardial infarction and "silent" myocardial infarction in RA compared with non-RA matched controls

Outcome	Multivariable odds ratio (95% confidence interval)
MI and subsequent hospitalisation	3.17 (1.16-8.68)
"Silent" MI	5.86 (1.29-26.64)

Adapted from (75)

1.4.2 Heart failure

Heart failure (or congestive cardiac failure (CCF)), is a physiological state where cardiac output is insufficient to meet the body's requirements. There are 4 grades of heart failure based on clinical symptoms as defined by the New York Heart Association (NYHA). These range from NYHA grade I (no symptoms or limitation of physical activity) to NYHA grade IV (unable to carry out physical activity without discomfort, plus symptoms of fatigue, palpitations or dyspnoea at rest) (76).

1.4.2.1 Heart failure in patients with rheumatoid arthritis

It has previously been shown that patients with RA are twice as likely to develop CCF than those without the disease (77). Data from a retrospective cohort from Rochester, Minnesota, demonstrated a higher cumulative incidence of heart failure after incident RA than those without the disease; 34% versus 25.2% ($p<0.001$) (77). At any particular age the incidence of heart failure in patients with RA was approximately twice the incidence in non-RA subjects, HR 1.87, (95% CI 1.47-2.39). The risk of heart failure was noted to be higher in RF positive RA patients (HR 2.59,

95% CI 1.95-3.43) compared with RF negative RA patients (HR 1.28, 95% CI 0.93-1.78).

Compared with non-RA subjects, RA patients with heart failure were less likely to be obese, be hypertensive, have a history of IHD and display typical signs and symptoms of the condition. RA patients with heart failure were more likely to have a preserved ejection fraction (≥50%) (78).

An echocardiographic study assessed 226 UK patients with RA, 65% of who were female. Definite left ventricular systolic dysfunction (LVSD), as defined by a left ventricular ejection fraction of <40%, was found in 5.3% of the study population, a standardized prevalence ratio of 3.2 (95% CI 1.65-5.59). By comparing these results with local population estimates, the authors extrapolated that LVSD was 3 times more common in patients with RA (79).

In patients with RA who developed new-onset heart failure, the proportion with a significantly elevated ESR was highest in the 6 month period immediately before diagnosis. The proportion with anaemia also peaked in this 6 month period. These results suggest that inflammatory stimuli may be involved in the initiation of heart failure in RA (80).

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a cardiac neurohormone released mainly from cardiomyocytes in response to left ventricular volume expansion and pressure overload (81). It can be used as a biomarker for heart failure (82). 171 consecutive RA patients without CCF were given the anti-TNF drug adalimumab and serum NT-proBNP measured simultaneously on stored baseline and 16-week samples. Circulating NT-proBNP decreased significantly after 16 weeks of adalimumab therapy by approximately 18% (p=0.004) (83). These interesting results are contrary to previously published concerns that TNF therapy may worsen left ventricular function in RA patients and if anything raises the possibility that TNF therapy may lessen CV risk.

1.4.2.2 Heart failure and tumour necrosis factor

TNF, along with other inflammatory molecules, is known to alter cardiac function through a number of mechanisms (84). Levine's group was one of the first to document the significantly elevated levels of TNF in a cohort of patients with chronic heart disease compared with controls (85). However, clinical trials to evaluate the efficacy of TNF therapy in patients with NYHA class II or greater heart failure were halted prematurely owing to the lack of clinical benefit and worsening of the patient's conditions (86) (87). An initial case series of 47 patients with new onset or exacerbated heart failure secondary to anti-TNF prompted a review of prescribing protocols (88) and guidelines incorporated heart failure as an exclusion to therapy. The British Society for Rheumatology (BSR) recommend that anti-TNF therapy should not be used in NYHA Grade III or IV heart failure and used with caution in NYHA Grade I or II heart failure. Anti-TNF should be discontinued if heart failure develops or worsens while on treatment (54).

1.4.3 Hypertension

Hypertension is one of the most important modifiable risk factors for the development of CVD, heart failure and cerebrovascular disease (66) (89), affecting approximately 1 billion individuals worldwide (90). The British Hypertension Society (BHS) has defined hypertension as ≥140 millimetres of mercury (mmHg) for systolic, ≥90mmHg for diastolic blood pressure (BP) and / or the use of anti-hypertensive medication (91). Different categories for BP have been further defined including "optimal" and "normal" recordings; these are outlined in Table 1.6. The National Institute for Clinical Excellence (NICE) and BHS have published joint guidelines for drug therapy and escalation (92) (93). Antihypertensive drug therapy has been proven to reduce the risk of stroke (by up to 40%), CHD (20% reduction in MI), heart failure (by greater than 50%) and total mortality (94) (95) (96). Predictive models, based on data from the Physicians' Health and Women's Health Study, have shown that lower levels of BP predict lower event rates for CVD and cerebrovascular disease. Both systolic and diastolic BP were significantly associated with event rates ($p<0.001$) in males, whereas only systolic BP was predictive in females ($p<0.001$) (97).

The Hypertension Optimal Treatment (HOT) study found that the lowest incidence of major CV events occurred at a mean diastolic BP of 82.6mmHg and the lowest risk of CV mortality at 86.5mmHg. The addition of aspirin reduced CV events by 15% (p=0.03) and of MI by 36% (p=0.002). (98).

Table 1.6 – Classification of blood pressure according to the British Hypertension Society

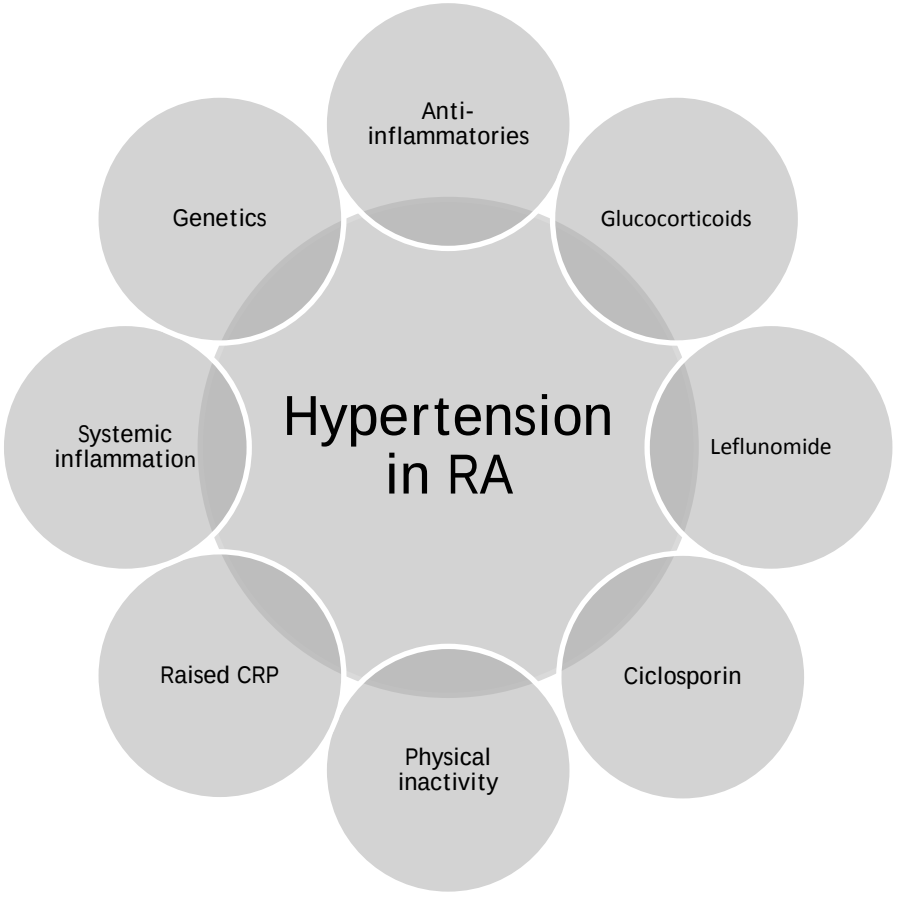
Category	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Blood pressure		
Optimal	<120	<80
Normal	<130	<85
High / normal	130-139	85-89
Hypertension		
Grade I (mild)	140-159	90-99
Grade II (moderate)	160-179	100-109
Grade III (severe)	>180	>110
Isolated systolic hypertension		
Grade 1	140-159	<90
Grade 2	>160	<90

Adapted from (91)

1.4.3.1 Hypertension in rheumatoid arthritis

The documented prevalence of hypertension in RA patients in the literature has varied widely. Panoulas and colleagues' extensive review on the subject suggests that from community-based populations, the prevalence of hypertension in RA patients is in the range 52-73% and in secondary care studies from 62-70.5% which is higher than the general population prevalence in the UK (99). Contributing factors to hypertension in patients with RA are illustrated in Figure 1.4.

Figure 1.4 – Potential factors contributing to hypertension in patients with rheumatoid arthritis



Adapted from (99)

Panoulas' own study of 400 consecutive RA patients identified hypertension in 70.5% of patients; of those 61% were prescribed anti-hypertensive therapy but 39% were previously undiagnosed and therefore untreated. Only 21.8% of patients on treatment were said to be adequately controlled (100). Hypertension has been found to be more prevalent in RA patients with medium dose (i.e. ≥7.5 milligrams (mg) per day) and long term exposure to glucocorticoids compared to RA patients with no or limited exposure to steroids (101). Target organ damage secondary to raised BP is highly prevalent, as found in a study of over 200 RA patients (102).

The Dutch Behandel Strategieën (BeST) study was a multicentre randomised clinical trial of DMARD-naïve patients with active RA of less than 2 years duration (103). In all 4 treatment strategies of the trial, systolic and diastolic BP were lower in those patients with a DAS28 of ≤2.4 compared with those with a higher DAS28 (104). Interestingly, those treated with the anti-TNF drug infliximab demonstrated an additional decrease in BP. The BeST study was not designed to look at blood pressure and as such the single BP measurements taken and the method of assessment may have led to inconsistencies.

Potential pro-inflammatory properties of angiotensin II have been described in the literature (105) and so it is of interest that studies involving RA patients prescribed angiotensin II receptor blockers have demonstrated a significantly lower ESR than RA controls (106).

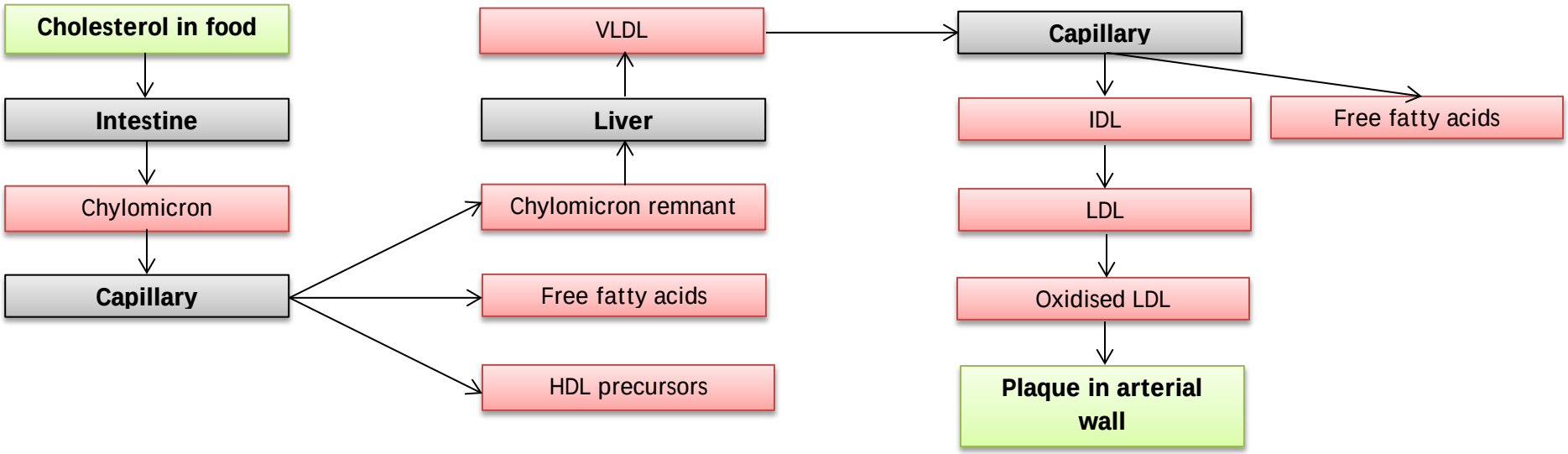
While there are no specific randomised controlled trials of hypertension management in RA, Panoulas and colleagues have published valuable guidance on the prevention, diagnosis, risk stratification and management on this subject. This adds to the literature available on management of the general population with hypertension. It is recommended that all patients with RA be assessed for additional CV risk factors to allow for stratification of risk alongside BP recordings. Anti-hypertensive therapy should be started after exclusion of drug causes (as detailed in Figure 1.4) as well as any other indicated CV therapies. All patients with RA should have their BP checked every time they attend primary or secondary care, or at least every 6 months (99).

1.4.4 Lipids

Chylomicrons and chylomicron remnants are the precursors of the various cholesterol subsets. The so –called "bad cholesterol" comprises: very low-density lipoprotein (VLDL) cholesterol measuring around 70 nanometres (nm), intermediate-density lipoprotein (IDL) cholesterol (40nm), and low-density lipoprotein (LDL) cholesterol (20nm). High-density lipoprotein (HDL) cholesterol measures around 10nm and is classified as "good cholesterol" – transporting fat back to the liver for excretion or to be passed to other tissues (107). An overview of the cholesterol pathway is illustrated in Figure 1.5. It is well established that elevated total cholesterol (TC) and low levels of HDL cholesterol are predictive of vascular event risk. The ratio of TC: HDL cholesterol is incorporated into many CV risk algorithms (108). Hyperlipidaemia is defined as elevated TC or LDL cholesterol, while dyslipidaemia refers to alterations of individual lipid components.

Figure 1.5 - Cholesterol synthesis pathway

Adapted from (107)



VLDL = very low-density lipoprotein, HDL = high-density lipoprotein

IDL = indeterminate-density lipoprotein, LDL =low-density lipoprotein

1.4.4.1 Lipids and rheumatoid arthritis

Hyperlipidaemia appears to be less common in RA patients than controls (109), however dyslipidaemia may affect up to half of RA patients (110) and is present in early disease. Blood bank samples from future RA patients had an average 4% higher TC, 9% lower HDL-cholesterol and 17% higher triglyceride levels compared with matched controls ($p \leq 0.05$) at least 10 years before the onset of symptoms (111). Alterations in lipid profile are well documented in RA literature; TC and LDL-cholesterol tend to fall in the presence of high levels of inflammation alongside a reduction in HDL-cholesterol (112). Reduced HDL-cholesterol and elevated Lipoprotein (a) correlate with elevated CRP levels and therefore with inflammatory activity in RA (113).

1.4.4.2 Lipids and disease modifying anti-rheumatic drugs

Anti-rheumatic therapies may have an effect on lipid levels. A study of 100 patients with active RA, randomised to either oral hydroxychloroquine or IM gold found that former was associated with a significant rise in HDL-cholesterol with no change in triglyceride levels (114).

1.4.4.3 Lipids and anti-tumour necrosis factor therapy

Infliximab has been shown to significantly increase TC and HDL-cholesterol in patients with RA, (115) (116) as has adalimumab (117). Further studies suggest that treatment with anti-TNF results in an increase not only in HDL-cholesterol but also other lipid moieties, including TC and LDL-cholesterol and perhaps triglycerides (118) (119). Such changes in lipid levels might be the predictable response to attenuation of inflammation; in untreated RA, reductions in HDL-cholesterol, LDL-cholesterol and TC have been noted (120). Moreover, these changes mirror lipid profile modifications associated with other pathologies and conditions that involve inflammation or infection, such as sepsis, cancer, trauma or post-operative state (121) (122) (123).

Qualitative changes in lipid particles during inflammation complicate further interpretations, but it seems as if TNF blockade reverses many of the anti-atherogenic effects of inflammation upon HDL particles (124) (125). The reduction

of inflammation seen in patients with severe RA given biologic therapy may be expected to cause a rise in lipid levels: TC, LDL-cholesterol and HDL-cholesterol and possibly triglycerides (126).

1.4.4.4 Lipid lowering therapy

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are also known as statins. They have been shown to substantially reduce CV morbidity and mortality (127). However, while their effects on lipid modulation are well described, it has also been demonstrated that statins may have anti-inflammatory properties. For instance, the Trial of Atorvastatin in Rheumatoid Arthritis (TARA) study was a randomised double-blind placebo-controlled trial in which 58 patients with RA were randomised to 40mg atorvastatin and 58 patients with RA randomised to placebo (128). By 6 months there was a significant improvement in DAS28 with statin therapy (reduction of 0.5 points) compared with placebo. CRP declined by 50% ($p<0.0001$) and ESR by 28% ($p=0.005$). The authors suggest that although statins would not be appropriate for first line disease-modifying therapy they could be a helpful adjunct.

Subsequently, Jick et al published a case-control study which evaluated whether statins were associated with a protective effect on the development of RA. Patients with hyperlipidaemia who were taking statins were less likely to develop RA than untreated patients (OR 0.59, 95% confidence interval 0.37-0.96) (129). Finally, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study reported in 2008. Apparently healthy patients without hyperlipidaemia but with elevated high sensitivity CRP (hsCRP) were chosen, but those with RA excluded. Rosuvastatin at 20mg once daily significantly reduced the number of major CV events compared with placebo (130).

1.4.5 Obesity and cardiovascular disease

Traditionally, obesity has been defined using body mass index (BMI): weight in kilograms (kg) divided by the square of height in metres (m^2). A normal BMI is classified as 20-24.9 kg/m^2. However, this measure does not take into account muscle mass, fat mass or fat distribution. The worldwide case-controlled

INTERHEART study assessed the relationship of BMI and waist to hip ratio (WHR) with risk of MI. Even at low levels of BMI, increased WHR resulted in an increased risk of MI; results were consistent to both sexes and different ages (131). A meta-analysis of over 250,000 patients identified an increased risk for total mortality in those patients with a low BMI of <20kg/m^2 (RR 1.37, 95% CI 1.32-1.43) and increased risk of CV mortality (RR 1.45, 95% CI 1.16-1.81). Patients who were overweight or mildly obese (BMI 25-34.9 kg/m^2) had no increase in total or CV mortality. The authors suggest this could be as a result of BMI poorly differentiating between body fat and lean mass (132).

1.4.5.1 Obesity and cardiovascular disease in rheumatoid arthritis

RA is associated with changes in body composition. Physical inactivity leads to an accumulation of body fat while activation of inflammatory pathways can cause muscle degradation. Therefore a patient with true "rheumatoid cachexia" exhibits low muscle mass and high fat mass (133). Kremers et al found that RA patients with a low BMI at time of time of diagnosis had a significantly higher risk of CV death (HR 3.34, 95% CI 2.23-4.99) compared with non-RA patients with a normal BMI; after adjusting for age, sex, personal cardiac history, smoking, diabetes, hypertension and malignancy (73). Those with a normal BMI at diagnosis who subsequently lost weight also had a higher risk of CV death (HR 2.09, 95% CI 1.50-2.92) than those who maintained a normal BMI during follow-up

Increasing BMI was found to be associated with increased CVD risk independently of many confounders in a study of 378 RA patients (22 from the original cohort of 400 were excluded because of a concomitant diagnosis of cancer).The authors suggest that RA-specific BMI categories may better identify patients in whom weight-loss would improve CV risk (134) and that BMI cut-off points should be reduced by 2kg/m^2 to better predict body fat from a BMI score in an RA patient (135).

1.4.6 Exercise, cardiovascular disease and rheumatoid arthritis

Exercise can provide significant health benefits in both the general population and some "at risk" subpopulations. It has been proven to reduce obesity (136), dyslipidaemia (137), diabetes (138) and is effective in preventing acute coronary

syndromes (139). Exercise rehabilitation programmes remain an important component in the management of a patient post-MI or acute coronary syndrome (140). A substantial review by Metsios and colleagues assessed the value of exercise interventions in patients with RA with regards to disease-related characteristics (141). They conclude that exercise is effective in reversing some of the joint damage in RA patients but that relatively little information exists on the role of exercise in the modification or management of CVD in inflammatory joint disease.

1.4.7 Hyperuricaemia, cardiovascular disease and rheumatoid arthritis

Patients with gout or asymptomatic hyperuricaemia can have clinical and biochemical abnormalities of metabolic syndrome including insulin resistance, obesity and hyperlipidaemia. All of these are linked to atherosclerosis and reduced life-expectancy (142). Although RA is not traditionally associated with hyperuricaemia (143), Panoulas and colleagues found that serum uric acid levels were significantly higher in RA patients with CVD compared to those without ($p=0.001$) and this was maintained after correction for CVD risk factors, physical function and use of diuretics and statins (OR 1.36, 95% CI 1.04-1.79, $p=0.025$) (144). The same author found that a 1mg per decilitre increase in serum uric acid was associated with a 1.6 increased odds of being hypertensive (145), thought likely due to vascular smooth muscle proliferation, activation of the renin-angiotensin system and salt sensitivity (146). Additionally, uric acid has been found to be a strong independent predictor of renal dysfunction in RA (147).

1.4.8 Renal function, cardiovascular disease and rheumatoid arthritis

Using the CARRÉ study cohort, Dutch researchers confirmed that in RA patients, renal dysfunction as demonstrated by a low glomerular filtration rate (GFR) was associated with higher risk of CVD which was independent of traditional CV factors; (OR 1.30 (95% CI 1.14-1.149) per 5 millilitre (ml)/minute/1.73m^2 decrease in GFR) (148). To describe in an alternative way, a 5ml/minute reduction in GFR was associated with a 30% increase in CV event rate over the 3 year follow up of the study.

In a subsequent cross-sectional single-centre study of 400 consecutive RA patients in whom 68% of patients had an estimated glomerular filtration rate (eGFR) of <90ml/minute/1.73m^2 and 13% had an eGFR of <60ml/minute/1.73m^2, linear regression was used to assess the independence of the associations between eGFR and other variables. There were significant associations between eGFR and age ($p<0.001$), TC ($p=0.022$), serum uric acid ($p<0.001$) and the presence of extra-articular disease ($p=0.040$). The authors suggest that renal dysfunction is common within an RA cohort and is associated with classical CV risk factors (149).

1.4.9 Biologic registry data on cardiovascular disease in rheumatoid arthritis

A number of large registries of patients with rheumatic conditions receiving biologic therapies have been established, with aims of producing long-term data on efficacy and toxicity.

1.4.9.1 Swedish registry data

In 2005, Jacobsson and colleagues from the South Swedish Arthritis Treatment Group (SSATG) published available data on the first incidence of CVD related events and deaths in patients included in their registry (150). The age-sex adjusted incidence rate of first CV event among the anti-TNF treated patients (13 events including deaths in a cohort of 531) was 14 per 1000 person-years (95% CI 5.7-22.4) compared with the anti-TNF naïve group (85 events including 12 deaths in a cohort of 543), 35.4 per 1000 person-years (95% CI 15.5-55.4). However, the small sample size did not allow for subgrouping for individual CV events and data on lipid profiles, smoking status and BP were lacking in this report.

1.4.9.2 British registry data

The British Society of Rheumatology Biologics Register (BSRBR) run a UK-wide, prospective, observational study of patients commencing anti-TNF therapy, with a comparator group of biologic-naïve patients with active RA. Specific outcomes with regard to first MI and stroke are detailed in Table 1.7 (151) (152). First-line analysis of the data confirmed a reduced rate of MI and stroke in patients receiving anti-TNF compared with those individuals only treated with DMARD. Additionally, anti-TNF "responders" had an even lower incidence of first MI.

Table 1.7- Incidence rates per 1000 person-years (and 95% confidence interval) of first MI and stroke in DMARD and anti-TNF treated groups from the BSRBR

	DMARD group (n= 2170)	Anti-TNF group (n=8659)	
MI	5.9 (3.4-9.4)	4.8 (3.7-6.1)	
		Responder	*Non-responder*
		3.5 (2.5-4.9)	9.4(5.5-15.0)
Stroke	9.9 (5.3-16.9)	3.9 (2.9-5.3)	

Anti-TNF responder group, n=5877. Anti-TNF non-responder group, n=1638.

Adapted from (151) (152)

Thus information presented from registry databases has demonstrated results that broadly support the hypothesis that anti-TNF therapy might lessen CV risk, potentially through a reduction in inflammatory load.

1.4.10 EULAR recommendations for cardiovascular disease risk management

Given the strong and consistent evidence linking inflammatory disease with increased CV risk, EULAR formed a group to develop evidence-based recommendations for CV risk management in patients with RA and other forms of inflammatory arthritis – such as PsA and ankylosing spondylitis (AS). The objectives of the group were to identify and critically appraise evidence for specific CV interventions aimed at lowering CV risk, to develop specific recommendations on the basis of a literature search for CV risk assessment and to determine future research goals. The recommendations for CV management in RA, PsA and AS, as published in 2010 are summarised in Table 1.8 (153).

Table 1.8 – EULAR's recommendations for managing cardiovascular risk in RA, PsA and AS

Recommendations
1. RA should be considered a condition with higher risk for CVD
2. Adequate control of disease activity lowers the CV risk
3. CV risk assessment using national guidelines recommended for all patients with RA and repeat assessment if therapy changes
4. Risk score models should be adapted for patients with RA by introducing a multiplication factor of 1.5 if patient meets 2 out of 3 criteria: Disease duration > 10 years, RF or ACPA positive, presence of certain extra-articular features
5. TC: HDL-cholesterol used if SCORE assessment used
6. Intervention carried out as per national guidelines
7. Statins, angiotensin converting enzyme inhibitors and / or angiotensin-II blockers preferred treatment options
8. Caution with prescribing most NSAID and COX2 inhibitors, especially if history of CVD or presence of CV risk factors
9. Use the lowest possible dose of corticosteroids
10. Recommend smoking cessation

SCORE= Systemic Coronary Risk Evaluation Adapted from (153)

1.4.11 Mechanisms for increased cardiovascular risk in rheumatoid arthritis

Inflamed synovium and unstable atherosclerotic plaque are very similar in a number of respects. In both diseased tissues, elevated levels of cytokines such as TNF, IL-6, IL-12, IL-15 and IL-18 have been observed, reflecting local stimulation of macrophages by activated T cells. TNF, IL-6, complement immune complexes, acute phase reactants and lipid particles have all been shown to be implicated in endothelial activation and destabilisation of atheromatous plaques (154).

Additionally, T cells implicated in the pathogenesis of atherosclerosis are predominately of TH1 or TH17 phenotypes, which are similar to the pattern seen in active RA (155). Both lesions contain an exaggerated matrix response and involve local cellular components; in RA: synovial fibroblasts, chondrocytes and osteoclasts and in atherosclerosis: vascular smooth muscle, fibroblast and endothelial cells (156). These similarities suggest possible mechanisms whereby patients with RA develop an increased risk of atherosclerosis and early death. The increased background level of chronic inflammation might confer predisposition to CVD and / or augment its pathogenesis, hence putting the individual at greater risk of developing an acute coronary syndrome or suffering secondary complications thereafter.

The concepts of endothelial dysfunction, arterial stiffness and acute-phase reactants are explored further in Section 1.5.

1.5 CARDIOVASCULAR DISEASE – ATHEROGENESIS AND FURTHER ASSESSMENTS

1.5.1 Biology of the atherosclerotic plaque

The first stage in development of an atherosclerotic plaque is endothelial dysfunction which can develop due to numerous causes including smoking and RA. As a consequence, the endothelium becomes more permeable, to lipids for example, and becomes pro-coagulant rather than anti-coagulant. The subsequent inflammatory response results in the entry of inflammatory and muscle cells as well as foam cells and the formation of fatty streaks. As the lesion progresses, a fibrous

cap forms, which consists of smooth muscle cells and a collagen matrix which separates the atherosclerotic plaque from the arterial lumen. Atherosclerotic plaques can be graded from Type I to Type V (c), as per the American Heart Association criteria (157). Types IV and V (a) atherosclerotic plaques have a high extracellular lipid content and are very prone to rupture and acute thrombosis; this is the event which initiates coronary thrombosis and subsequently causes an MI. The micro-anatomical features of an atherosclerotic plaque at risk of disruption (the so-called "vulnerable plaque") include a large lipid core, high macrophage content and a thin cap. Two major determinants of plaque vulnerability include the core size and cap thickness – neither of these is related to absolute plaque size or to the degree of stenosis (158).

1.5.2 Endothelial dysfunction

Endothelial dysfunction has been suggested as a possible early event in the evolution of atherogenesis, as well as a surrogate marker for risk of CVD. A range of techniques aimed at estimating endothelial function have been employed, including plethysmography, ultrasonography-determined flow-mediated dilation (FMD), laser Doppler imaging with iontophoresis and more recently, measures of pulse wave velocity (PWV) or arterial stiffness and pulse wave analyses. Biomarkers of endothelial dysfunction have been identified: vascular cell adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1 and endothelial cell adhesion molecule (ECAM)-1.

1.5.2.1 Endothelial dysfunction in rheumatoid arthritis

Reduced forearm blood flow has been demonstrated in studies where patients with either RA or systemic vasculitis were compared with healthy controls (159, 160) hence showing that patients with inflammatory rheumatic conditions have evidence of endothelial dysfunction. A study assessing the effect of infliximab on endothelial function in 11 patients with RA demonstrated a significantly increased FMD ($p=0.018$), along with significant reduction in ESR ($p=0.04$), CRP ($p=0.08$) and DAS ($p=0.002$) (161). An study of infliximab in RA patients confirmed an increased FMD after first intravenous infusion (3.7% versus 17.5%, $p<0.01$) with similar results after second and third infusions (162). Along with hsCRP, IL-1, IL-6 and TNF α, these

biomarkers were higher in RA patients than in controls ($p<0.001$). VCAM1 has been associated with increased carotid intima media thickness (cIMT), $p=0.02$ (163). CRP has been demonstrated to be independently associated with microvascular dysfunction in RA (164).

1.5.3 Arterial stiffness

Arterial stiffness can be measured non-invasively. PWV is a measure of the speed at which the arterial pressure wave travels – higher values are associated with established CV risk factors and with CV mortality (165). Augmentation index (AIx) is a quantitative index of systemic arterial compliance that refers to the difference between the first and second systolic peak of the central waveform, expressed as a percentage of the pulse pressure (166).

1.5.3.1 Arterial stiffness in rheumatoid arthritis

Analysis of the association between RA and arterial stiffness has confirmed an increased aortic (carotid to femoral) PWV compared with controls ($p=0.005$) and similar increased brachial (carotid to radial) PWV ($p=0.02$) with no significant difference in AIx or augmentation pressure observed (167). Recently, Avalos et al demonstrated that patients with a disease duration greater than 10 years had a significantly higher AIx than patients with a disease duration of less than 5 years ($p=0.008$) or controls ($p<0.001$) – an association which remained significant even after adjusting for CV risk factors ($p=0.02$) (168). Etanercept has been shown to reduce arterial stiffness (169). Patients who respond to anti-rheumatic therapy demonstrate an improvement in microvascular function (170). Australian researchers found that pulse wave analysis was a more sensitive measure of endothelial dysfunction than brachial artery (171). Infliximab at dose 3mg/kg has been shown to improve PWV in 26 RA patients treated over a 56 week period; there was no significant change in cIMT measurement or the presence of carotid artery plaque (172).

1.5.4 Carotid intima-media thickness

Non-invasive B-mode ultrasonography of the carotid arterial system provides information on lumen diameter and intima-media thickness. It can be regarded as an indicator of generalised atherosclerosis (173). In 1997, a group from The Netherlands provided evidence that increased cIMT was associated with future CV and cerebrovascular events (174), further data from the United States of America (USA) corroborated this (175).

1.5.4.1 Carotid intima-media thickness in rheumatoid arthritis

cIMT is increased in patients with inflammatory conditions such as RA (176) (177), PsA (178), systemic lupus erythematosus (179) and also primary Sjögren's syndrome (180); it has been demonstrated that cIMT severity is associated with inflammatory burden and disease duration (181).

It would appear that increased cIMT develops early on in the evolution of RA. In one study, 79 patients from Sweden with newly diagnosed RA (and less than 12 months of symptoms) were enrolled in a prospective study of CVD co-morbidity. They were matched by age and gender with 40 controls. At baseline evaluation there was no significant difference in cIMT or endothelial dependent FMD. However, by 18 months there was a significant increase in cIMT in RA patients ($p<0.05$). The cIMT thickness in both groups was associated with traditional CV risk factors. There was no relationship with disease activity markers in the RA group (182).

A recent smaller study of 30 RA patients commencing anti-TNF (14 infliximab, 16 etanercept) compared their disease progression and cIMT over the course of a year's therapy with 10 controls. Anti-TNF therapy was associated with a significant reduction in cIMT after 1 year of treatment ($p>0.0001$); a significant correlation between DAS and cIMT was also found ($r=0.435$, $p<0.05$) (183). Well-designed and larger trials are needed to establish the true extent of benefit of anti-TNF therapies on cIMT.

1.5.5 Insulin sensitivity

In the general population, insulin resistance is an recognised risk factor for CV disease and type 2 diabetes mellitus and contributes to the metabolic syndrome (184) (185).

1.5.5.1 Insulin sensitivity in rheumatoid arthritis

The issue of insulin sensitivity and RA as a potential mechanism contributing to increased CV risk has been investigated. In one study 94 RA patients were assessed to identify which factors regulate glucose metabolism (186). hsCRP was used to identify grading of inflammation: the authors defined hsCRP <1.92mg/litre (l) as "low-grade" inflammation and hsCRP >1.92mg/l as "high-grade" inflammation. Patients with "high-grade" inflammation had a higher BMI (p=0.03), greater waist circumference (p=0.01), lower HDL cholesterol p=0.03) and a higher frequency of impaired fasting glucose or diabetes (p=0.3) than those with "low-grade" inflammation. In addition, homeostatic model assessment of insulin resistance (HOMA-IR) associated positively with waist circumference (p<0.0001), hsCRP level (p=0.004), DAS28 (p=0.04) and ESR (p=0.02). The data from this study demonstrates that patients with higher levels of hsCRP had increased insulin resistance and reduced beta-cell function compared to those with "low-grade" inflammation. The association of higher BMI and waist circumference with "high-grade" inflammation was an unexpected finding, given that in the general population obesity contributes to both insulin resistance and reduced beta-cell function.

Additionally, patients with RA treated with oral steroids or pulsed parenteral steroids demonstrated a decreased insulin sensitivity and as such authors suggest that steroids may contribute to increased CV risk (187). Similarly, several studies have confirmed an association between obesity, increased insulin sensitivity and elevated TNF levels (188) (189).

1.5.6 C-reactive protein and cardiovascular disease

Increased CRP has been identified as an independent CV risk factor in the general population (190). Additionally, this acute phase reactant has been demonstrated to be independently associated with microvascular dysfunction in RA (164). CRP level at the time of diagnosis of inflammatory arthritis is an important predictor of subsequent death from CVD. For instance, when approximately 500 patients with RA were followed up for over 10 years by Goodson et al, an elevated CRP of ≥5mg/l predicted death from CVD as per univariate analyses: HR 3.9 (95% CI 1.2-13.4) for men and HR 4.22 (95% CI 1.4-12.6) for women (191). However, adiposity is also independently associated with CRP levels in female patients with RA and may act as a confounder in the estimation of RA disease activity when using CRP as a surrogate marker for systemic inflammation (192). Goodson's study did not take BMI into account in multivariate analysis.

1.5.7 Genetics of rheumatoid arthritis relating to cardiovascular risk

Work by Goodson et al has shown that excess mortality in the early years of an inflammatory polyarthritis is limited to those who are seropositive for RF. This is seen in all-cause mortality (SMR males 1.51 and females 1.41) as well as CV mortality (SMR males 1.34, females 2.02) (193). A further study confirmed these findings (194). In addition, the presence of ACPA antibodies is associated with increased cIMT (195).

Moreover, a study by Farragher and colleagues identified that possessing two copies of the shared epitope alleles predicted death from all causes (HR 1.57, 95% CI 1.1-2.2) and from CVD (HR 1.68, 95% CI 1.1-2.7). An interaction between smoking, shared epitope alleles and ACPA was associated with the greatest risk of death from CVD (HR 7.81, 95% CI 2.6-23.2). No association of PTPN22 gene and mortality was identified (196).

Additional studies in the GWAS-era have looked at other potential genetic links between RA and predisposition to CVD. Reports have suggested that polymorphism in the transforming growth factor- beta 1 (TGFB1) gene is associated with heart disease in the general population. Chen and colleagues have found that the

interaction between smoking and polymorphism in the TGFB1 gene may influence the risk of IHD and MI in RA patients (197).

Levels of IL-6 are high in RA and thought to be an important contributor to the development of CVD. A study of 135 patients with RA demonstrated an increased risk of CVD in those carrying the IL6-174C-allele (p=0.041) as well as significantly higher levels of IL-6 (p=0.028) (198) but this genetic profile was not associated with an increased prevalence of hypertension (199). A further study by the same group found an increased prevalence of raised endothelin (ET)-1 levels in hypertensive RA patients and the presence of a ET-1 gene locus (EDN1) haplotype was associated with a 3-fold increased adjusted odds of being hypertensive(200). Additionally, the authors found that TGF8697-allele carriers had a significantly increased prevalence of hypertension compared with CC homozygotes (p=0.023) (199).

1.6 CARDIOVASCULAR DISEASE RISK ASSESSMENT

UK guidelines recommend that all people aged 40-74 years should have a CVD risk assessment performed (201). Further details expanding those individuals potentially at increased risk are detailed in Table 1.9. This then allows the individual to be placed in one of 3 groups; low, moderate or high as outlined in Table 1.10. However, debate exists on a number of issues: should lifetime risk or 10-year risk be the end-point, CVD versus CHD as the defined event and whether non-laboratory-based risk scores could be developed (i.e. without inclusion of cholesterol levels) (202).

Table 1.9 – Who should have their cardiovascular disease risk calculated?

Identification of individuals
1. All adults aged 40-74 years with no pre-existing CVD
2. Strong family history: Father or brother with MI or CVA ≤55 years old Mother or sister with MI or CVA ≤60 years old
3. 1st degree relative with hereditary lipid disorder

Adapted from (201)

Table 1.10 – Classification of 10-year cardiovascular disease risk

Grading of CVD risk	% 10-year risk of developing CVD
Low	<10%
Moderate	10-20%
High	>20%

As per NICE guidelines, treatment is currently offered if the 10-year CVD risk score is >20% or if the individual has pre-existing CVD, diabetes or chronic kidney disease. RA and connective tissue diseases are mentioned as important factors for the clinician to bear in mind but do not feature in the list of "high priority" conditions. The treatments which are offered are listed in Table 1.11.

Table 1.11 – Therapies offered if high 10-year cardiovascular risk calculated

Options for therapy
Drug therapy
Lipid lowering drugs
Anti-hypertensives
Lifestyle modifications
Smoking
Weight
Diet
Alcohol
Exercise

Adapted from (201)

The calculators and tools used are evolving, and are described in more detailed in sections 1.6.1 - 1.6.4 below. Comparison between factors used to calculate the 3 main scores are detailed in Table 1.12.

1.6.1 Framingham score

The Framingham score is a standard and original score for calculating 10-year risk of CVD. It is based on a mainly Caucasian population in Massachusetts, USA. It takes into account age, gender, HDL-cholesterol and TC, smoking and systolic BP. It may over-predict risk in populations with low observed CHD mortality. Similarly it may under-predict in populations with high observed CHD mortality: British Asians, familial hypercholesterolaemia, the socially deprived, severe hypertension, left ventricular hypertrophy , type I diabetes and type II diabetes with nephropathy (202) (203) (204).

1.6.2 Joint British Societies Coronary Risk Prediction score

The Joint British Societies Coronary Risk Prediction (JBSCRP) score, most recently updated in 2005, is based on Framingham data. It divides by gender, smoking status and diabetes. It takes into account age (<50 years, 50-59 years or ≥60 years), TC: HDL-cholesterol and systolic BP. The predicted 10-year risk includes all atherosclerotic CVD: acute coronary syndrome, cerebrovascular disease, exertional angina and peripheral vascular disease (108). The JBSCRP is based on untreated levels of BP. CVD risk is higher than indicated in the charts for positive family history, triglycerides >1.7millimoles (mmol)/l, BMI ≥30kg/m^2, females with premature menopause, men with HDL <1mmol/l, women with HDL <1.2mmol/l, impaired glucose tolerance and certain ethnic minorities.

1.6.3 ASSIGN score

Recently published CV risk assessment tools have incorporated social deprivation. Assessing CV risk using Scottish Intercollegiate Guideline Network (SIGN) guidelines to assign preventative treatment (ASSIGN score) has been designed to incorporate deprivation into CV risk in a Scottish population. It was developed from the Scottish Heart Health Extended Study which followed up 12,000 patients over 10 years and recorded morbidity and mortality (205). This study highlighted that a large discrepancy in coronary risk existed in Scottish men and women which was related to their social status but inadequately explained by conventional CV risk factors.

ASSIGN calculates the 10-year percentage risk of developing CVD in those disease-free at recruitment (206). The calculated score is an actual or "absolute" risk. Two novel additional risk factors were added which were unique compared to other risk prediction tools. These are family history (of CHD or stroke in a parent or sibling aged less than 60 years old) and a measure of social deprivation, the Scottish Index of Multiple Deprivation (SIMD) as described in Section 1.10.3. The ASSIGN score therefore is based upon: (1) age at last birthday, (2) gender, (3) SIMD to 2 decimal places, (4) family history, (5) diabetes, (6) current cigarette smoking (if yes, number per day), (7) systolic BP, (8) TC to 2 decimal places, (9) HDL-cholesterol to 2 decimal places. With the addition of family history and social deprivation, ASSIGN may score higher than Framingham, especially in older females. It has been

adopted by SIGN and the Scottish Government as the most appropriate CV risk score for current use in the Scottish population.

Reviewers felt that ASSIGN, based on an intermediately-sized sample, is representative of the general population but that reporting studies do not comment on external validation (207). Although it may still overestimate CV risk, it is still thought to be marginally better than Framingham (202).

Table 1.12 – Comparison of factors included in cardiovascular risk calculations

Framingham (208)	**JBSCRP** (108)	**ASSIGN** (209)
Age	Age	Age
Gender	Gender	Gender
Smoking	Smoking	Smoking
Systolic BP	Systolic BP	Systolic BP
TC	TC: HDL	TC
HDL	Diabetes	HDL
		Diabetes
		Family history
		Deprivation score

1.6.4 Other cardiovascular disease risk scores

Other CV risk scores which exist include the Adult Treatment Panel III, the Reynolds Risk Score, QRISK and SCORE (202).

QRISK2, a calculator for an individual's risk of developing diabetes, CHD or stroke over the next 10 years, was developed between 1993 and 2008 from patients living in England and Wales (210). It built upon the original QRISK algorithm (211) by incorporating family history, ethnicity and deprivation (using the Townsend index,

as described in Section 1.10.1). The authors felt that at 10 years, Framingham over-predicted CV risk by up to 35% and ASSIGN by 36%, compared to 0.4% in QRISK (211). However the data used to create the QRISK and QRISK2 calculations was validated from the same population as it was originally derived, leading to concerns of a "home advantage" and need for further validation. QRISK and QRISK2 were derived from databases of GP attendees, which allowed the inclusion of substantial number of patients but were not random representative samples of the population.

The Systemic Coronary Risk Evaluation (SCORE) chart is a European CVD risk assessor (212). In addition to standard CV risk information, it classifies European countries as either low risk (Belgium, France, Greece, Italy, Luxembourg, Portugal, Spain and Switzerland) and the remainder as high risk. SCORE has previously been mentioned in the context of the EULAR recommendations on managing CV risk in inflammatory arthritis (see Section 1.4.10 and Table 1.8).

1.7 ANTI-INFLAMMATORY DRUG THERAPY

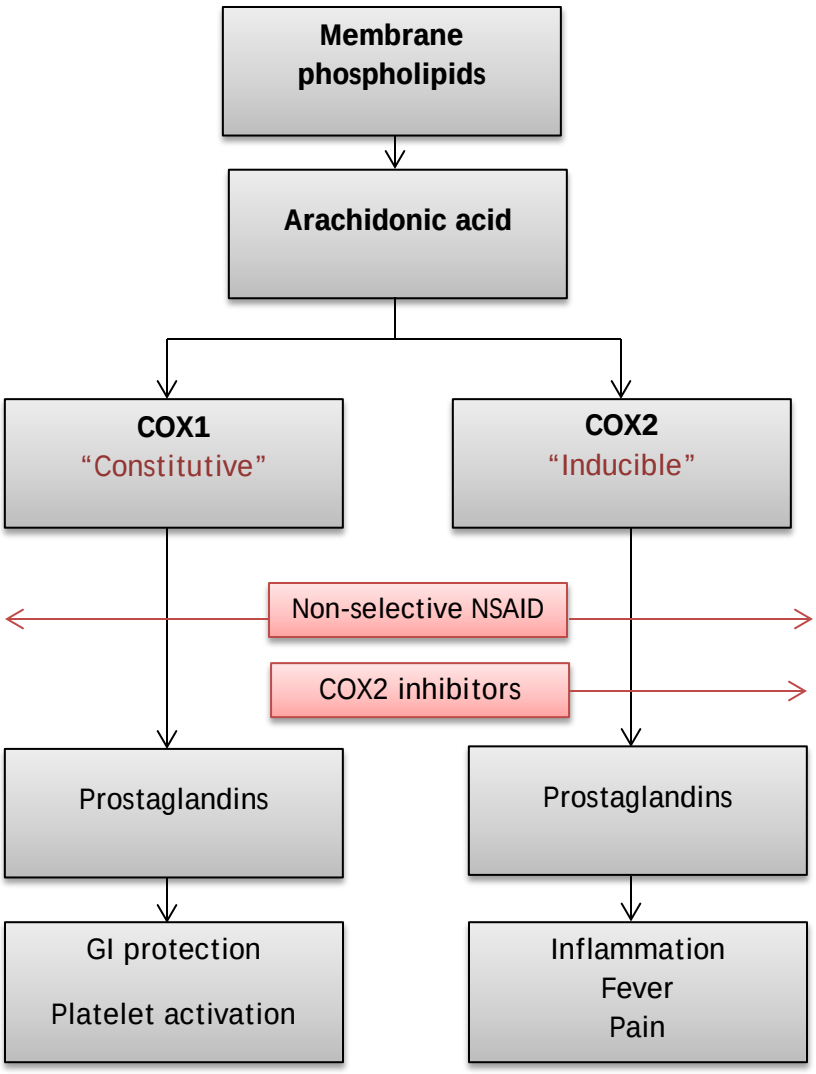
The first synthesis of acetylsalicylic acid was performed in 1853, a compound later to be named aspirin in 1899 by the company, Bayer. This was the first non-steroidal anti-inflammatory drug (NSAID) (213). Anti-inflammatories have long been prescribed for symptoms of arthralgia, dental pain, dysmenorrhoea and headache, amongst other uses. They continue to be one of the most commonly prescribed classes of medication worldwide (214) and have been a cornerstone therapy in the treatment of symptoms of RA, OA and other arthritides.

NSAID cross the placenta and manufacturers recommend avoiding their use during pregnancy. In particular they should be avoided during the third trimester: there is a risk of closure of the foetal ductus arteriosus and concern of subsequent persistent pulmonary hypertension in the new-born; additionally, labour may be delayed and prolonged by their use (215).

1.7.1 Prostaglandin biosynthesis and the role of cyclooxygenase

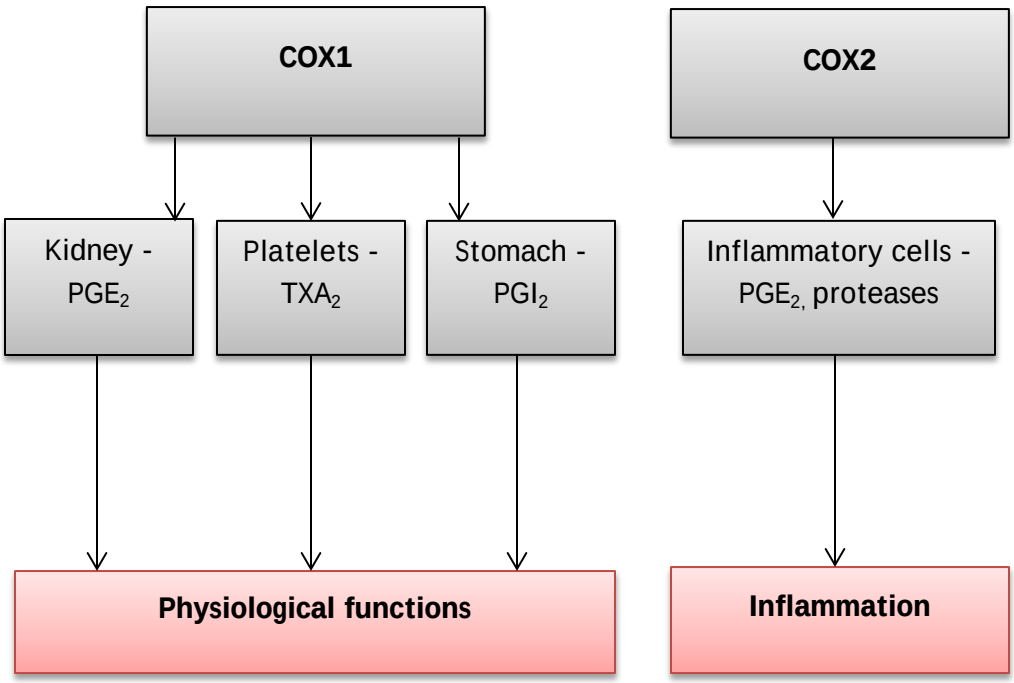
Both the benefits and harm from anti-inflammatories are due to the inhibition of cyclooxygenase (COX) of which there are 2 isoenzymes, COX1 and COX2. Both COX isoenzymes have a hydrophobic tunnel, through which the substrate accesses the active site. The tunnel is larger in the COX2 isoenzyme with a side pocket, a property exploited in the development of specific COX2 inhibitors (216). COX is the rate-limiting enzyme which converts arachidonic acid to the labile intermediate prostaglandin (PG) H2. This is in turn converted to thromboxane A2 by thromboxane synthease, prostacyclin by prostacyclin synthase and other prostaglandins including PGE2 and PGD2. Thus the metabolism of prostaglandins is markedly altered by COX inhibition, as illustrated in Figures 1.6 and 1.7 (216) (217).

Figure 1.6 – Mechanism of anti-inflammatory drug action



Adapted from (217)

Figure 1.7 – Differential prostanoid synthesis and action



PGE_2 = prostaglandin E_2, PGI_2 = prostaglandin I_2, TXA_2 = thromboxane A_2

Adapted from (216), (217)

1.7.1.1 Non-steroidal anti-inflammatory drug action

All NSAID reduce PG production and result in relief of hyperalgesia (increased sensitivity to pain) caused by tissue damage, see Figure 1.5. Individual compounds vary in their chemical structure and ability to block COX1 in preference to COX2. These drugs reach high concentrations in inflamed tissues, leading to an inhibition of prostaglandin synthesis at the desired site of action. However they also reach high concentrations in other organs and in the blood, leading to the side effects reported by patients and noted by clinicians (218). As the CV benefits of aspirin come from its inhibition of COX1, it would seem sensible to conclude that NSAID would not increase the risk of CV events. However, a near-complete inhibition of platelet COX1 is required for this cardio-protective benefit, something that no non-aspirin NSAID can achieve in a sustained fashion. No placebo-controlled trial has studied the CV risk of non-selective NSAID therapy. Few of the studies that these meta-analyses are drawn from on this subject record the indication for NSAID use.

Although the size of the overall patient risk appears small, the absolute risk may be considerable due to the large number of patients prescribed NSAID.

1.7.1.2 COX2 inhibitor action

The primary property of this group of drugs is the inhibition of the COX2 enzyme; they are more than 100 times as selective in their ability to inhibit COX2 as traditional non-selective NSAID (213). Initial research suggested that COX1 was continuously expressed in most tissues while COX2 was induced in inflammation, as illustrated in Figure 1.5. However, recent evidence has shown that COX2 is constitutively expressed in several organs and systems, including the kidney, central nervous system and vascular wall (219) and that it can adversely influence the prostacyclin: thromboxane (anti-thrombotic: thrombotic) ratio in the vascular wall (220). This may then promote platelet aggregation and atherosclerosis, resulting in an increased burden of CV toxicity.

First generation COX2 inhibitors include celecoxib and rofecoxib, second generation include etoricoxib and valdecoxib. Celecoxib has a half-life of 11-16 hours, etoricoxib has a half-life of 19-32 hours (221).

1.7.1.3 Effectiveness of COX2 inhibitors

One of the first studies of the effectiveness of COX2 inhibitors was published in 1999 by Emery et al, who studied the efficacy of celecoxib in patients with RA (222) .Three hundred and twenty six patients received celecoxib 200mg twice daily and 329 diclofenac 75mg twice daily for 24 weeks. There was no difference between the 2 drugs for visual analogue pain score, EMS or CRP. However, the mean number of swollen and tender joints did decrease over the course of the study in both treatment groups; but again, no significant difference was seen between the 2 cohorts. Overall, the authors concluded that celecoxib was as equally effective as diclofenac in managing inflammatory joint disease, with lower GI side-effects. Subsequently, a systematic review of the efficacy of celecoxib compared with another non-selective NSAID or placebo demonstrated that the drug therapies were equally efficacious (223).

1.7.2 Co-prescription of aspirin with either NSAID or COX2 inhibitor

The use of aspirin in primary and secondary cardio-protection is well established in clinical practice. Aspirin irreversibly inhibits COX1-mediated production of thromboxane A2; a single 325mg dose of aspirin results in 89% inhibition of platelet COX1 and a 650mg dose results in >95% inhibition (224). NSAIDs reversibly inhibit COX1 in platelets and so the subsequent effects on platelet aggregation depends on the half-life of the individual anti-inflammatory. It has been demonstrated that ibuprofen given before aspirin inhibited the beneficial effects of irreversible platelet inhibition (225). On the basis of this and other studies, the United States Food and Drug Administration (FDA) issued an advisory notice in September 2006 regarding the co-administration of aspirin and ibuprofen (226). They recommend that aspirin should be taken before any NSAID or that the doses should be given separately.

In 2002, Wilner et al had published results of a double-blind placebo-controlled trial of 16 healthy volunteers assigned to celecoxib 400mg daily or placebo for 4 days (227). On day 5, aspirin 325mg plus either celecoxib 200mg or placebo was prescribed. No significant difference between the two groups in thromboxane inhibition was noted. Additionally, there was no significant difference in the effect of aspirin on platelet aggregation due to adenosine diphosphate, collagen or arachidonic acid between the groups. The overall summary was that celecoxib does not have an effect on the aspirin effects of platelet function.

The population impact of any possible interaction is potentially large. In a sample of the general population prescribed COX2 inhibitors, analysed by Cox et al (228), 48% were co- prescribed aspirin, 43% paracetamol and interestingly 10% were also prescribed a non-selective NSAID. Unsurprisingly the use of aspirin was associated with increased with increasing age.

Levesque documented the relative risk of first acute MI in a cohort of over 113,000 elderly patients (229). Patients prescribed celecoxib with or without aspirin were identified. There was no significant difference in adjusted RR of acute MI in those who were or were not prescribed aspirin alongside celecoxib. This differs from the low-dose rofecoxib group who showed a significantly reduced risk of acute MI if

prescribed aspirin (RR 1.0, 95% CI 0.77-1.28); the same was not true for patients on high-dose rofecoxib (RR 2.36, 95% CI 1.27-4.39). It is worth pointing out that the actual number of patients who had an acute MI while on aspirin was small and conclusions drawn from this study should be guarded.

1.7.2.1 Effects of aspirin plus anti-inflammatories on the gastrointestinal system

There have been concerns of the adverse GI effects of COX2 and aspirin versus NSAID and aspirin and whether gastric protection agents are required. Endoscopic studies have shown that the incidence of GI ulcers did not differ between patients on celecoxib and aspirin combination compared with those on NSAID, aspirin and proton pump inhibitor (230). It has therefore been suggested that the use of low-dose aspirin with COX2 inhibitors is preferable to non-selective NSAID given similar anti-inflammatory properties, superior GI tolerability and absence of interaction with aspirin (231). Rahme et al found that the combination of celecoxib and aspirin was less likely to be associated with hospitalisation for GI events than NSAIDs with aspirin (HR 0.62, 95% CI 0.48-0.80) (232) (233). Hospitalisation rates for GI events were similar for celecoxib plus aspirin as NSAID without aspirin (HR 1.01, 95% CI 0.81-1.25). A limitation of this and many similar studies was that over-the-counter data for aspirin were not available.

1.7.3 Anti-inflammatory medication and the risk of myocardial infarction

1.7.3.1 NSAID and the risk of myocardial infarction

The risk of MI has been shown to vary between individual NSAID. The relative risk of MI with diclofenac, ibuprofen and naproxen as documented in 4 key meta-analyses is detailed in Table 1.13. All showed an increased risk of MI with diclofenac, with RR varying from 1.4 to 1.63, but not with naproxen (234) (235) (236) (237).

Large individual studies have reported on the risk of MI and subsequent death with traditional non-selective NSAID. Gislason et al have shown that ibuprofen or diclofenac use was associated with a 1.5 to 2.4-fold increased risk of death. Again, a strong dose-response relationship was identified. No information was given on concomitant use of aspirin in this study (238).

Table 1.13 Comparison of relative risk of acute myocardial infarction with diclofenac, ibuprofen and naproxen from key meta-analyses

Lead author	Relative risk of myocardial infarction		
	Diclofenac	**Ibuprofen**	**Naproxen**
Hernandez-Diaz (234) • **16 trials**	1.44 (95% CI 1.32-1.56)	1.07 (95% CI 1.02-1.12)	0.98 (95% CI 0.92-1.05)
Kearney (235) ◊ **? number of trials**	1.63 (95% CI 1.12-2.37)	1.51 (95% CI 0.96-2.37)	0.92 (95% CI 0.67-1.21)
McGettigan (236) • **17 case control, 6 cohort trials**	1.40 (95% CI 1.16-1.7)	1.07 (95% CI 0.97-1.18)	0.97 (95% CI 0.87-1.07)
Singh (237) • **14 trials**	1.38 (95% CI 1.22-1.57)	1.11 (95% CI 1.06-1.17)	0.99 (95% CI 0.88-1.11)

• NSAID users versus non-users, ◊ NSAID versus placebo

1.7.3.2 COX2 inhibitors and the risk of myocardial infarction

The concern regarding increased risk of MI with COX2 inhibitor use stems from the year 2000 and an early study of major GI events, the Vioxx Gastrointestinal Outcomes Research (VIGOR) study. This showed an unexpected 5-fold increase in the risk of acute MI with subjects on rofecoxib, compared with naproxen (239). At the time of publication, many hypothesized that this was due to the cardio-protective effects of naproxen. However, in September 2004 the manufacturers of rofecoxib withdrew the drug from worldwide sale based on the safety findings of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study (240). This study demonstrated that long-term use of rofecoxib 25mg daily was associated with a 3.5% incidence of MI or ischaemic stroke compared with placebo in patients with no pre-existing history of CVD (1.9% of placebo group, $p<0.001$). The Adenoma Prevention with Celecoxib (APC) study group published an interim analysis of their data, which showed that celecoxib at supra-therapeutic doses was also associated with an increased risk of CV thrombotic events (241).

Subsequently, the FDA (242), European Agency for the Evaluation of Medicinal Products (243) and the UK-based Medicines and Healthcare Products Regulatory Agency (MHRA) (244) have all issued recommendations that COX2 inhibitors should not be prescribed for those with pre-existing IHD or cerebrovascular disease.

Just as the risk of MI has been shown to vary between individual NSAID, the relative risk of MI varies between individual COX2 inhibitors and a clear dose-dependent relationship has been shown. The relative risk of MI with celecoxib and rofecoxib use as documented in 3 meta-analyses is detailed in Table 1.14 (234) (236) (245).

Kearney et al (235) performed a meta-analysis of data on vascular events from randomized controlled trials of COX2 inhibitors (not included in Table 1.13). Studies included in this meta-analysis which compared a COX2 inhibitor with a traditional NSAID (91 trials) showed no significant difference in the risk of vascular events (RR 1.16, 95% CI 0.97-1.38). The risk of high dose celecoxib was confirmed in a pooled analysis of nearly 8000 patients enrolled in 6 placebo-controlled trials. Authors Solomon et al demonstrated a clear increased risk of all CV events including acute MI with increasing doses of celecoxib: HR 1.8 (95% CI 1.1-3.1) for

celecoxib 200mg twice daily and HR 3.1 (95% CI 1.5-6.1) for the supra-therapeutic dose of 400mg twice daily (p=0.0005) (246).

While the above large studies and subsequent meta-analyses focused on the risk of celecoxib and rofecoxib use, etoricoxib, a second-generation COX2 inhibitor has been studied in more detail in recent years. In the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study the authors assessed the relative CV toxicity of diclofenac and etoricoxib in patients with OA or RA, aged 50 years or older (247). Patients with CV and GI risk factors were included in order to assess the widest possible range of comorbidities. Data were pooled from 3 separate pharmaceutical industry-sponsored randomised double-blind controlled trials, totalling approximately 25,000 OA and 10,000 RA patients. Nearly 17,000 patients received etoricoxib with slightly less receiving diclofenac. The numbers of thrombotic CV events were similar in both groups, with higher risks of upper GI events in the diclofenac group (0.97 per 100 patient-years). The lack of placebo group limits the ability to determine the absolute CV risks of the two drugs.

The MEDAL data vary from the results of Andersohn et al's nested case control study of over 3000 patients with an MI and nearly 14,000 controls. The authors documented that etoricoxib use was associated with a RR of 2.09 for acute MI (95% CI 1.1-3.97). This compared with RR of MI with other COX2 inhibitors and NSAID as: ibuprofen 1.04, naproxen 1.15, diclofenac RR 1.37, any dose of rofecoxib 1.29 and celecoxib 1.56 (248).

Table 1.14 - Comparison of relative risk of acute myocardial infarction with celecoxib and rofecoxib from key meta-analyses

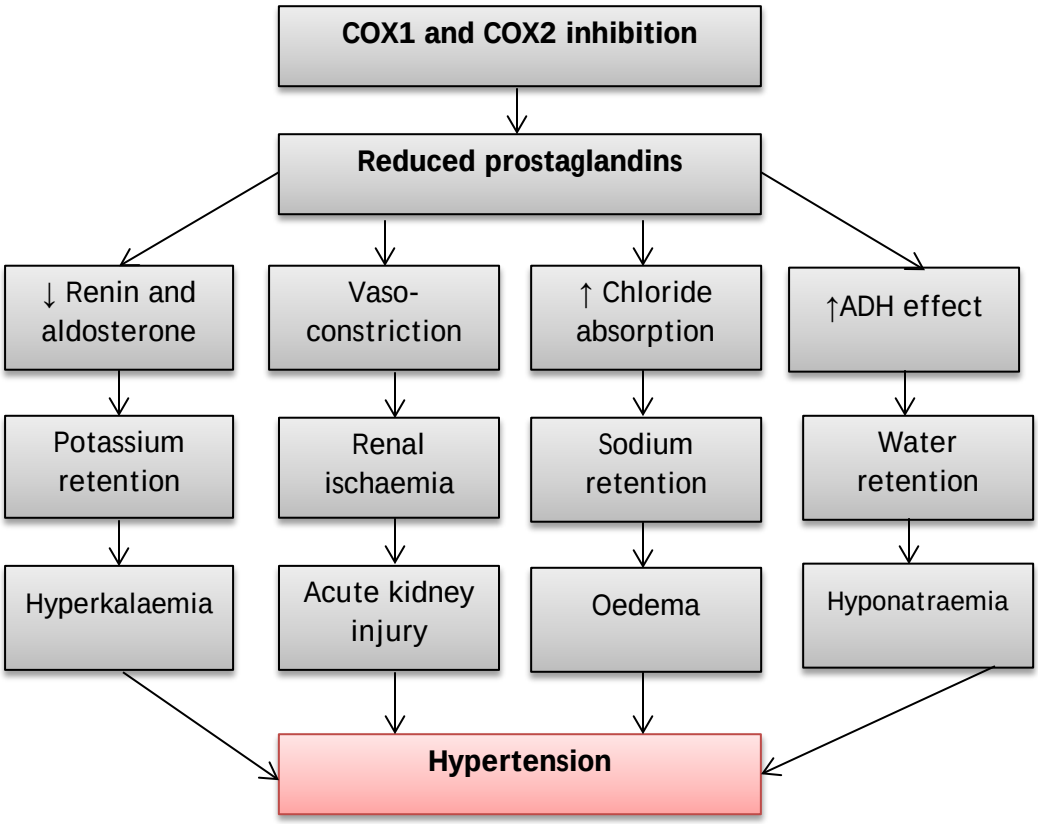
Lead author	Relative risk of myocardial infarction			
	Celecoxib	**Rofecoxib** Any dose	**Rofecoxib** ≤25mg/day	**Rofecoxib** >25mg/day
Hernandez-Diaz (234) • [16] trials	0.96 (95% CI 0.90-1.02)	1.26 (95% CI 1.17-1.36)	1.18 (95% CI 1.07-1.31)	1.78 (95% CI 1.36-2.34)
Jüni (245) □ 18 randomised,11 observational	-	2.24 (95% CI 1.24-4.02)	1.37 (95% CI 0.52-3.61)	2.83 (95% CI 1.24-6.43)
McGettigan (236) • **9 case control, 2 cohort studies**	1.06 (95% CI 0.91-1.23)	1.35 (95% CI 1.15-1.59)	1.33 (95% CI 1.00-1.79)	2.19 (95% CI 1.64-2.91)

• COX2 users versus non-users, □COX2 versus NSAID or placebo

1.7.4 Anti-inflammatory medication and hypertension

Hypertension is a common adverse event seen with NSAID and COX2 inhibitor use although the exact mechanism through which they may increase BP is not completely known. It has been speculated, however, that drug-induced vasoconstriction, effects on the renin-angiotensin system and direct effects on eGFR leading to a rise in urea and creatinine may all contribute (249) (250, 251) . Crucial to these mechanisms is the initiating event of prostaglandin inhibition as illustrated in Figure 1.8.

Figure 1.8 – Possible explanations why anti-inflammatory drugs may cause hypertension



ADH = anti-diuretic hormone

Adapted from (252) (250) (251)

The renal-related effects on BP are relatively rare in young and healthy people in whom the kidneys are usually able to compensate for the effects of NSAID or COX2 inhibitors on sodium and water retention. However, this process may be diminished in individuals with renal impairment, the elderly and those with CCF.

1.7.4.1 NSAID and hypertension

On average, most NSAIDs increase BP by 3-5mmHg (251) (253) (254). Even such a seemingly modest rise can significantly increase the frequency of CV events, including IHD and heart failure (255) (256). A systematic review of randomised controlled trials on the effect of at least 4 weeks therapy with NSAID demonstrated a mean systolic BP increase of 3.54mmHg with ibuprofen and 2.9mmHg with indomethacin users compared with placebo (257).

Moreover, many studies have demonstrated that NSAID lessen the anti-hypertensive effects of diuretics, beta blockers, angiotensin converting enzyme inhibitors (258) (254) (259). However, they do not seem to have any effect on the anti-hypertensive effects of calcium channel blockers (260) (261).

1.7.4.1 COX2 inhibitors and hypertension

In a meta-analysis of 19 randomised controlled trials, COX2 inhibitor use compared with placebo resulted in a weighted mean increase in systolic BP of 3.85mmHg and in diastolic BP of 1.06mmHg. This compares with an increase in systolic BP of 2.83 mmHg and diastolic BP of 1.34mmHg when COX2 inhibitor use was compared non-selective NSAID. COX2 inhibitors were associated with a non-significantly higher relative risk of causing hypertension compared with placebo (RR 1.61, 95% CI 0.91-2.84, p=0.10) and non-selective NSAIDs (RR 1.25, 95% CI 0.87-1.78, p=0.23) (262).

The Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation Trial (CRESCENT), a double-blind randomised trial of patients with OA, assigned individuals to celecoxib 200mg once daily, rofecoxib 25mg once daily or naproxen 500mg twice daily (263). Twenty four-hour ambulatory BP monitoring and arthritis efficacy measurements were carried out. The mean 24-hour systolic BP after 6 weeks of therapy was increased significantly in the rofecoxib group but not celecoxib or naproxen groups. The BP difference between rofecoxib and celecoxib

was 3.78mmHg (95% CI 1.18-6.38, p=0.005), between rofecoxib and naproxen 3.85mmHg (95% CI 1.15-6.55, p=0.005).

In a study of NSAID and COX2 inhibitor use in normal clinical practice, no significant increase in BP was noted for non-selective NSAID or celecoxib use in patients without prior history of hypertension. However, a significant risk of BP increase was seen with rofecoxib (OR 2.08, 95% CI 1.41-3.06) (264).

In a meta-analysis of 114 randomised double-blind clinical trials of COX2 inhibitors, rofecoxib was associated with an increased risk of hypertension (RR 1.55, 95% CI 1.29-1.85) whereas celecoxib was associated with lower risk of hypertension than controls (RR 0.83, 95% CI 0.71-0.97) (265).

A MEDAL study sub-analysis evaluated the hypertensive effects of etoricoxib and diclofenac. An increase in systolic BP was most highly associated with a prior history of hypertension (rise of 3mmHg, $p<0.0001$) and use of etoricoxib, compared to diclofenac ($p<0.0001$) (266).

In summary, initial studies documented that rofecoxib, more so than celecoxib, has been associated with an increase in BP readings. More recently, studies have shown an increase in BP with etoricoxib use. Consequently, guidance has been issued that BP should be monitored during the use of celecoxib or etoricoxib. In particular with etoricoxib, BP should be checked before treatment and 2 weeks after treatment initiation to ensure that BP control has not been substantially disrupted (215).

1.7.5 Anti-inflammatory medication and heart failure

It is well established that use of NSAID increases heart failure risk. For instance, a nested case-control study of 1396 cases of first admission to hospital for heart failure showed an overall 30% increased incidence in those prescribed NSAID versus the control group (267). The risk of hospitalisation varied with different NSAID (with higher risk seen with indomethacin and naproxen) and in the presence of comorbidities such as hypertension and diabetes. The authors postulate that this equates to one extra case per year of first heart failure-related hospital admission for every 1000 NSAID users aged 60 to 84 years.

Further supporting evidence for this association as well as extending the link to COX2 inhibitors comes from McGettigan and colleagues who conducted a case-control study to investigate the relationship between anti-inflammatory use and hospitalisation on due to CCF. Controls were subjects admitted to the same hospitals as the cases who did not have CCF. Anti-inflammatories had been taken by 23.6% of controls in the week prior to admission, 28.4% of first-time cases of CCF and in 15.5% of recurrent cases (p=0.0004 for difference). Adjusted relative risk for first admission with CCF was 1.1 for NSAID (95% CI 0.67-1.83), 1.29 for rofecoxib (95% CI 0.78-2.13) an 1.47 for celecoxib (95% CI 0.85-2.53) (268).

Finally, a population based retrospective cohort study identified 2256 patients over the age of 66 who were prescribed celecoxib, rofecoxib or NSAID after an index admission for CCF. The risk of death and recurrent CCF combined was higher in patients prescribed NSAID or rofecoxib than those prescribed celecoxib (HR 1.26, 95% CI 1.00-1.57 and HR 1.27, 95% CI 1.09-1.49 respectively) (269). This was borne out in an additional study of similar design (270).

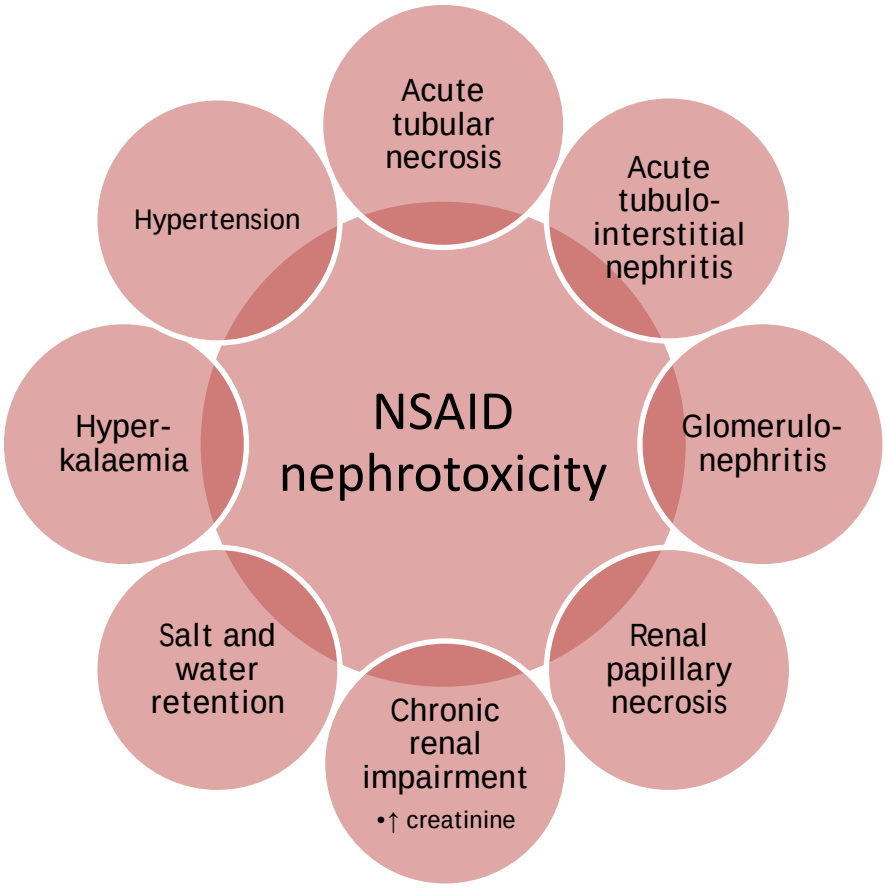
1.7.6 Anti-inflammatory medication and renal function

1.7.6.1 NSAID and renal function

A spectrum of nephrotoxicity has been documented with NSAID therapy and is illustrated in Figure 1.9.

A review by Koseki et al documented an elevated creatinine in 6% of early RA patients taking a NSAID (271). Researchers have studied the effects of NSAID withdrawal on renal function: 11 patients prescribed NSAID for more than 6 months had therapy withdrawn. There was a subsequent significant reduction of creatinine ($p<0.02$) but a less consistent, non-significant trend in urea reduction (272). Interestingly, the value of creatinine may underestimate renal function in RA patients due to the, often significant, muscle atrophy that can occur (273).

Figure 1.9 – Causative factors involved in NSAID-induced nephrotoxicity



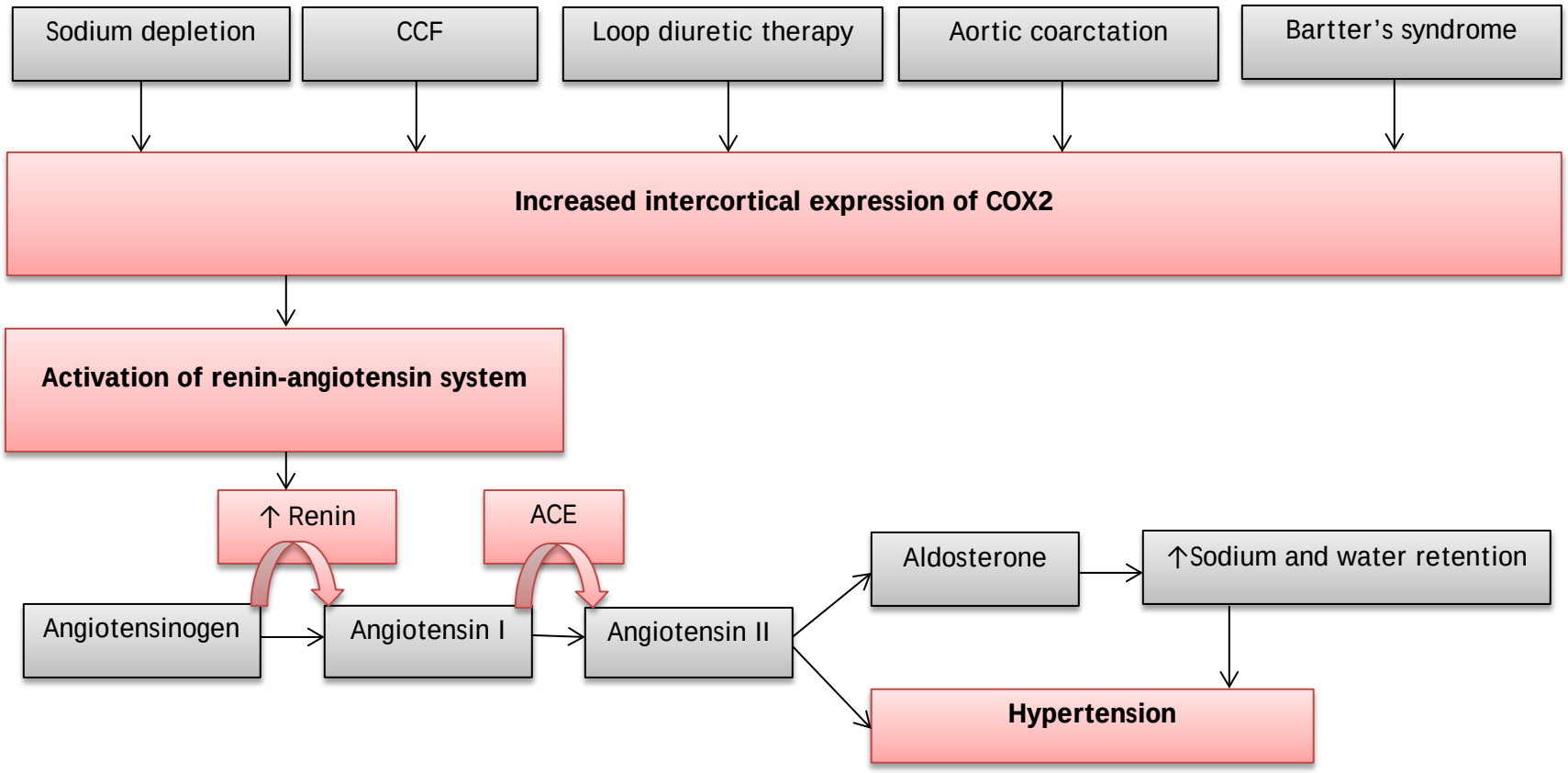
Adapted from (274)

1.7.6.2 COX2 inhibitors and renal function

The interactions between COX2 and the renal system are complex and not thought yet to be fully understood. COX2 is known to have critical roles at the cortical thick ascending limb of the loop of Henle, macula densa and in the medullary interstitium (250). Figure 1.10 illustrates proposed physiological interactions between COX2, the kidney and the renin-angiotensin system and builds further on the initial outline of why COX1 and COX2 inhibition is linked to hypertension (as illustrated in Figure 1.8).

Figure 1.10 – Proposed physiological interactions between COX2, the kidney and the renin-angiotensin system

Adapted from (250) (275) (276)



ACE= angiotensin converting enzyme

A comparable reduction in GFR was seen for both naproxen and celecoxib in a specific renal function outcomes study in an elderly population (252). Between-treatment difference in creatinine clearance or serum electrolytes was seen in a double-blind placebo-controlled study of 85 patients assigned to naproxen, etoricoxib or celecoxib (277). A meta-analysis of over 100 randomised placebo-controlled trials found that rofecoxib was the COX2 inhibitor mostly likely to cause renal dysfunction (RR 2.31, 95% CI 1.05-5.07) (265).

The British National Formulary suggests that NSAID and COX2 inhibitors should be avoided if possible in patients with renal dysfunction; if they are prescribed, caution is advised and a suggestion made to use the lowest possible dose for the shortest possible length of time (215).

In summary, COX2 inhibition can cause renal sequelae especially in volume depleted individuals and where there is reduced organ perfusion (275). Furthermore, COX2-induced hyperkalaemia is more likely in cases of pre-existing renal disease or if the patient is prescribed angiotensin converting enzyme inhibitor, angiotensin II receptor blocker or potassium-sparing diuretic (276).

1.7.7 Anti-inflammatory medication and gastrointestinal side-effects

1.7.7.1 NSAID and gastrointestinal side-effects

The systemic effects of NSAID are largely due to the inhibition of endogenous prostaglandin synthesis. When prostaglandins are inhibited there is a reduction in epithelial mucus, mucosal blood flow and mucosal resistance to injury (278).There is a spectrum of NSAID-related GI injury from subepithelial haemorrhages through to erosions and ulcerations. Additionally they can cause small-bowel ulceration, exacerbations of inflammatory bowel disease, significant haemorrhage and death (279). GI damage does not occur in all patients taking NSAID and is not readily predicted by symptoms. It is therefore important to attempt to identify individuals potentially at risk. Definite risk factors include: advancing age, previous history of GI ulceration, high doses of NSAID, use of multiple NSAID, comorbid conditions and concomitant use of steroids or anticoagulants. *Helicobacter pylori* infection, smoking and alcohol use are additional risk factors (213).

Serious GI complications occur in 1-4% of NSAID users per annum (213) (280). A large retrospective review of nearly 3000 cases of upper GI bleeding in Spain has given valuable real-life information on this clinical problem (281). 24% of the patients with bleeding had taken non-aspirin NSAID in the week prior to admission. Naproxen was associated with the highest risk of bleeding (RR 7.3, 95% CI 4.7-11.4). The combination of NSAID plus low-dose aspirin increased the risk still further (RR 12.7, 95% CI 7-23). The study identified that ibuprofen and diclofenac had the lowest risk profile of the traditional NSAID for upper GI bleed. Proton pump inhibitors have consistently been shown to be more effective than H2-receptor antagonists and prostaglandin analogues in the prophylaxis and management of GI damage in patients who require continuous NSAID therapy (282) and additionally are well tolerated with an excellent safety profile.

It is commonplace to prescribe cardio-protective low-dose aspirin to some patients at risk of CVD. This, in addition to NSAID therapy, increases the risk of acute upper GI bleeding from an OR of 4 for aspirin alone (95% CI 3.2-4.9) to 17.5 (95% CI 11.9-25.8) in combination with NSAID (283). The addition of a proton pump inhibitor to this combination reduces the OR to 1.1 (95% CI 0.5-2.6). Therefore, careful consideration of the addition of a proton pump inhibitor should be given to all patients prescribed NSAID and aspirin. A Cochrane review supports the safety of this approach (284). An additional potentially modifiable risk factor is *Helicobacter pylori* infection. Chan et al have shown that in the short term, *Helicobacter pylori* eradication decreases the incidence of peptic ulcer disease in patients who begin NSAID therapy (285).

1.7.7.2 COX2 inhibitors and gastrointestinal side-effects

A superior GI safety profile was at the crux of initial marketing of COX2 inhibitors, based on 2 large GI outcome studies (239) (286). The Successive Celecoxib Efficacy and Safety Study I (SUCCESS-I), a large multi-national randomized double-blind controlled trial, compared the upper GI safety of celecoxib with naproxen and diclofenac in a cohort of more than 13000 patients with osteoarthritis (287). Of the group randomized to celecoxib, 37.2% had GI symptoms compared to 40.3% in the NSAID group ($p<0.001$), with an OR for complicated upper GI side-effects of 6.02 (95% CI 1.5-34.57) in the NSAID group. Celecoxib was found to be as effective as traditional NSAID in efficacy for

treating OA symptoms. SUCCESS-I conclusively established the GI safety profile of celecoxib. Other large outcome studies have shown no difference in complicated GI events between etoricoxib and diclofenac (288).

The combination of COX2 inhibitor plus proton pump inhibitor has been evaluated in patients with an upper GI bleed secondary to NSAID-induced ulceration (289). Two hundred and seventy three patients were randomised to celecoxib plus omeprazole or placebo. None of the patients who received COX2 inhibitor plus proton pump inhibitor and 12 of the patients who received celecoxib alone had further bleeding (p=0.0004). A limitation of this study is the lack of NSAID comparator. Details of co-prescription of aspirin, in the context of CV risk, are also missing from data analysis.

The initial COX2 inhibitor studies assessing prevention of adenomatous polyps (APPROVe (240), APC (241) and Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) (290)) showed a reduction in rate of adenoma formation. It was these studies which documented the associated increased rate of CV events. Their withdrawal from the market meant that this avenue of chemoprevention was not further pursued.

It is vital to pay attention to the comparator NSAID in studies showing a GI safety advantage of COX2 inhibitors, as traditional NSAID vary in their risk of serious GI side effects. "GI toxic" NSAID such as naproxen are more likely to show a statistical significance over COX2 inhibitors, as in VIGOR study (239). This is in comparison with "less toxic" NSAID such as diclofenac, used in the MEDAL study (247). Head-to-head clinical trials may be required to highlight any differences between the GI safety profiles of individual COX2 inhibitors.

A 6 month double-blind trial randomised analysed over 4000 patients with RA or OA in 32 countries to celecoxib 200mg twice daily or diclofenac slow release 75mg twice daily plus omeprazole 20mg once daily (Celecoxib versus Omeprazole and Diclofenac in patients with Osteoarthritis and Rheumatoid arthritis, CONDOR) (291). 0.9% of patients receiving celecoxib and 3.8% of patients receiving diclofenac had an upper or lower GI event (HR 4.3, 95% CI 2.6-7.0, p<0.001). This is one of the first studies to assess for adverse events throughout the length of the GI tract. However, patients taking aspirin were excluded and the decision of presumed occult GI blood loss in an anaemic

patient, without confirming the source of the blood loss does limit full interpretations of the results. The study authors confirm that the trial was not designed nor powered to assess CV outcomes.

1.7.8 Anti-inflammatory medication and cerebrovascular disease

In the APC study, the number of nonfatal strokes within the placebo group was identical to the events in the celecoxib 200mg twice daily group (n=3). In the 400mg twice daily group, there were 5 nonfatal strokes (241).

However, there is convincing evidence linking anti-inflammatory use and increased risk of cerebrovascular disease. For instance, a subsequent large case-control study assessed nearly 500,000 patients from the UK GP research database between 2000 and 2004. The researchers found that current use of rofecoxib and etoricoxib was associated with significantly increased risk of ischaemic stroke (multivariate OR 1.71 and 2.38 respectively) and that this risk was dose-dependent (292). The risk was maintained even if the patient had no pre-existing history of cerebrovascular disease, hypertension or atrial fibrillation. It is, however, possible that the differences in stroke rates reflect the differential effect on BP of these drugs.

In addition, Haag et al followed 7636 patients from a prospective population-based Rotterdam Study, from baseline in 1991-1993 for incident stroke until 2004 (293). In the 70,000 person-years of follow-up, 807 patients developed a stroke. Current users of non-selective NSAID and COX2 inhibitors had a greater risk of stroke; adjusted HR 1.72 (95% CI 1.22-2.44) and adjusted HR 2.75 (95% CI 1.28-5.95) respectively. Naproxen and rofecoxib were associated with the greatest risk of stroke.

Nested case-control analyses were performed within the longitudinal American National Data Bank for Rheumatic Diseases (294). Two hundred and sixty nine cases of first-ever strokes were identified, 67 were ischaemic in aetiology. The OR for all types of stroke in RA was 1.64 (95% CI 1.16-2.30, p=0.005) and for ischaemic stroke 2.66 (95% CI 1.24-5.70, p=0.012). Ischaemic stroke was predicted by hypertension, MI, low-dose aspirin, health assessment questionnaire (HAQ) score and presence of total joint replacement. There was no association between anti-TNF therapy and ischaemic stroke. Roumie et al in a retrospective cohort study calculated the rate of stroke as 4.51 per 1000

person years in those not taking anti-inflammatory, 5.15 with rofecoxib, 4.66 with celecoxib, 4.05 with naproxen and 5.61 with indomethacin. None of the increase seen with non-selective NSAIDs was significant (295).

1.7.9 Anti-inflammatories and hepatic side effects

Diclofenac is principally metabolised in the liver and drug-induced hepatitis is a relatively commonly seen adverse effect (296). Hepatotoxicity is usually seen within 12 weeks of starting the causative drug and liver function abnormalities generally settle within 4-6 weeks of stopping the drug (297). A review of adverse drug reactions in France demonstrated that 14% of all NSAID-related reports were for abnormal liver function (298). Two lumiracoxib-related studies published in the Lancet in 2004 reported a reduction in GI ulcer complications with no apparent evidence of increased MI (299) (300). However in November 2007, this drug was withdrawn in the UK by MHRA (301). This was due to 159 reported episodes worldwide of adverse liver reactions attributed to this drug, two of which were fatal. In large-scale investigatory studies such as the Celecoxib Long-term Arthritis Safety Study (CLASS) and SUCCESS-I, there was no significant elevation in aminotransferases (286) (287). Traditional NSAID and COX2 inhibitors should be used in caution in patients with hepatic impairment due to the increased risk of GI bleeding, fluid retention and worsening of hepatic function. All anti-inflammatories should be avoided in severe liver disease (215). A report of a case / non-case analysis has shown that overall COX2 inhibitors are thought to have fewer hepatic side effects than NSAIDs (302).

1.7.10 Summary of anti-inflammatory side-effects and options for patients

A summary of the main side-effects of non-selective NSAID and COX2 inhibitors is detailed in Table 1.15. Patients who are felt to require an anti-inflammatory can have the options discussed with them based on their individual CV and GI risk, as outlined in Table 1.16.

Table 1.15 - Overview of anti-inflammatory side-effects

System	NSAID	COX2 inhibitor
Cardiovascular	Hypertension (257) (Fig 1.7)	Hypertension Etoricoxib and rofecoxib (262) (Fig 1.7)
	Myocardial infarction Diclofenac > ibuprofen (Table 1.13)	Myocardial infarction Rofecoxib > celecoxib (Table 1.14)
	Heart failure (267) (268)	Heart failure (268)
Renal	↑creatinine (252) (271) (277) (Fig 1.8)	↑creatinine (252) (265) (277) (Fig 1.9)
Gastrointestinal	Spectrum of GI side-effects Naproxen highest risk (279) (281)	Less GI side-effects than NSAID (239) (281) (286) (287)
Cerebrovascular	Risk of ischaemic stroke More so with naproxen (293)	Risk of ischaemic stroke Etoricoxib and rofecoxib (292)
Hepatic	Hepatic dysfunction Especially with diclofenac (296)	Overall fewer side-effects than NSAID (302)

Table 1.16 - Anti-inflammatory treatment options for patients

Patient risk status	Choices
No GI or CV risk	Ibuprofen, diclofenac, naproxen Can be used in combination with paracetamol / weak opioids Avoid concomitant use of aspirin with ibuprofen (226)
GI risk, no CV risk	Celecoxib (+/- proton pump inhibitor) (289) Ibuprofen + proton pump inhibitor
GI and CV risk	Assess each patient individually Avoid if possible / use lowest dose for shortest period of time

Adapted from (303)

1.8 MEDITERRANEAN-TYPE DIET

The Mediterranean region of Europe stretches from Portugal and Spain in the west, through the south-coast of France, Italy and finally to Greece and its numerous islands in the east, Figure 1.11. The temperate climate of the region has benefited farm-land, resulting in rich and fertile conditions for growing produce. A Mediterranean-type diet is typically rich in fruit, vegetables and legumes (FVL), with a moderate to high intake of fish, a low intake of dairy produce and red meat and a high intake of unsaturated fats, especially olive oil. The higher intake of fish than meat is likely a reflection of the previous high cost of meat and proximity to the sea to obtain seafood. This type of diet is usually complemented by a modest amount of alcohol, mainly in the form of red wine and almost always taken during meals. The content of this diet has remained fairly constant over time. Although different regions in the Mediterranean area have their own diet, it is valid to consider them as variations of a single entity (304).

Figure 1.11 – Map of the Mediterranean region

Image from: http://www.freeusandworldmaps.com/html/WorldRegions/WorldRegions.html

The characteristic diet of individuals living in the Mediterranean region contrasts starkly with that of Northern Europeans. The British diet suffers from a poor international reputation with a narrow range of heavy foods, high meat intake and is considered rather tasteless (305). The Scottish diet in particular has been shown to have a low ratio of polyunsaturated to saturated fats and low antioxidant content. These dietary traits are more pronounced in individuals who live in socially deprived areas (306).

A number of authors over the centuries have tried to alter the British mind-set on diet and food choices. One of the earliest recorded examples of this is the Italian Giacomo Castelvetro, who in 1614 tried to encourage Londoners to eat more fruit and vegetables similar to the dietary intake in his home-land (307). In the post-war years of the 1950s, Elizabeth David was formally credited with trying to transform post-war British eating habits with her publication of her book on Mediterranean foods (308).The Mediterranean-type diet has recently been recognized by the United Nations Educational, Scientific and Cultural Organisation (UNESCO) as a worthy example to be added to the worldwide Representative List of Intangible Cultural Heritage (309).

Over the last few decades much interest has been generated around the potential health gains, in particular to the CV system, of adhering to such a diet. A large number of studies have been undertaken to assess the benefits of this type of lifestyle intervention – both in epidemiological and controlled trial settings.

1.8.1 Mediterranean diet score

The Mediterranean diet score is a tool frequently used in studies to assess intake of component foods. It allows comparison between individuals, between cohorts (e.g. between countries) and between interventions (310) and is frequently used in epidemiological studies. The simplest version of the score varies from 0-9, more complex scores range from 0-55. It is based upon the analysis of completed food-frequency questionnaires (FFQ), a sample page excerpt of which is included in Appendix I and discussed further in Section 2.8. There are some concerns with using a FFQ to estimate adherence to a Mediterranean diet as it was originally developed to assess the intake of total energy and macronutrients (fat, protein, carbohydrates) and not individual components such as FVL consumption (311).

One point is given for intake at or above the gender-specific median amount of the components considered healthy. One point is given for intake less than the median for components considered unhealthy, such as meat and dairy products. An additional point can be gained for alcohol consumption within a specific range. Higher values of this score indicate greater adherence to a Mediterranean diet.

1.8.2 Overall benefits of a Mediterranean-type diet

One of the first studies of the potential benefits of adherence to a Mediterranean diet was carried out by Trichopoulou and colleagues in the early 1990s (310). The subjects comprised 182 residents (equal numbers male and female) of 3 Greek villages. Median age at recruitment was 75.4 years. Dietary habits were recorded over a 2 year period and on revisiting the villages 3 years later, 53 of the subjects had died. Food diaries were reviewed and when a Mediterranean diet score applied, a 1-point increase was associated with a 17% reduction in overall mortality (rate ratio 0.83, 95% CI 0.69-0.99) and a greater than 50% reduction per 4-point increase.

Trichopoulou expanded her initial work by prospectively studying over 22,000 healthy Greek adults aged 20-86 years. When their Mediterranean-diet scores were reviewed, a 2-point increase was associated with a 25% reduction in total mortality, over a median 44 months follow-up (312).

The Healthy Ageing: a Longitudinal study in Europe project followed up over 2000 apparently healthy men and women aged 70-90 years in 11 European countries. Adherence to a Mediterranean-type diet was associated with a lower risk of all-cause 10-year mortality: HR 0.77, 95% CI 0.68-0.88 (HR adjusted for age, gender, years of education, BMI and other factors). This was compared to moderate alcohol consumption (HR 0.78, 95% CI 0.67-0.91), physical activity (HR 0.63, 95% CI 0.55-0.72) and non-smoking (HR 0.65, 95% CI 0.57-0.75) (313).

A recently published meta-analysis of prospective cohort studies assessed the relationship between adherence to a Mediterranean diet, mortality and incidence of chronic diseases in a primary prevention setting. This covered over half a million subjects and over 33,000 deaths. Greater adherence to a Mediterranean diet was associated with a significant reduction in overall mortality (9%), mortality from CVD (9%), incidence of or mortality from cancer (6%) and incidence of Parkinson's Disease and Alzheimer's Disease (13%) (314).

It is not certain whether adhering to a Mediterranean diet has any benefits for those aged over 80 years (315) as an increase in Mediterranean diet score in this age group was not associated with any reduction in overall mortality.

1.8.3 Cardiovascular benefits of a Mediterranean-type diet

The Seven Countries Study by Keys et al is comparable to the Framingham Study in being one of the largest, longest and most important epidemiological studies of recent times. The aim of the Seven Countries Study was to discover if diet could influence life expectancy. Over 11,000 men aged 40-59 years from the USA, Japan, Finland, Italy, Greece, The Netherlands and the former Yugoslavia were studied. None had previous history of heart disease or cancer. Marked differences were seen in the different regions after 15 years of follow-up. The male residents of the Greek island of Crete, who had a plentiful intake of fruit, vegetables, fish and olive oil, had a death rate of 38 per 10,000. Finland, by comparison, with a diet rich in meat, saturated fat and refined sugar, had a death rate of over 1200 per 10,000. Age, BP, smoking status, serum cholesterol,

and the ratio of monounsaturated: saturated fat accounted for 96% of the differences between death rates for CHD. This ground-breaking work became the template for other prospective studies of a Mediterranean-type diet (316) (317).

A number of studies have assessed the impact of this type of diet on CV mortality in non-Mediterranean Europeans, Americans and Australians. Trichopoulou's research team took their work to 9 European countries and assessed over 74,000 patients aged greater than 60 years, with no prior history of CVD, stroke or cancer. Here, a 2-point increase in Mediterranean-diet score was associated with a statistically significant 8% increase in survival (95% CI 3-12%) (318). Similar results were observed in the USA where over 200,000 males and 166,000 females were followed up prospectively for 5 years – reduced CV mortality was noted in patients with higher Mediterranean-diet scores (multivariate HR 0.78, p value for trend <0.001) (319). Two Australian studies have also demonstrated reduced mortality with higher Mediterranean diet scores (320) (321). Interestingly, the latter of those 2 studies demonstrated that migrants to Australia from the Mediterranean area had a lower mortality than native-born Australians.

A Mediterranean-type diet is usually rich in fish and this specific aspect has been studied with regards to CVD. Researchers have demonstrated a reduced incidence of sudden cardiac death (multivariate RR 0.48, 95% CI 0.24-0.96, p=0.04), in male patients with no prior history of IHD or stroke, who consumed more than one fish containing meal per week, when compared with men who consumed fish less than once per month (322). A significant 29% reduction in mortality in patients in the fish group was demonstrated.

There can be little doubt that adherence to a Mediterranean-type diet and / or a diet rich in fish is associated with significant long-term health benefits.

1.8.3.1 Use of a Mediterranean-type diet in patients with pre-existing cardiovascular disease.

While the above studies were epidemiological and looked at populations as a whole, recent work has focussed on asking patients to adhere to a specific diet after a primary CVD episode. The Lyon Diet Heart Study followed 605 patients who were randomly assigned to either a low-fat (n=302) or a Mediterranean-type

diet (n=303) after a first MI (323). The study was terminated early due to a significant reduction in cardiac events in the Mediterranean group: 1.24 cardiac deaths or non-fatal MI per 100 patients per year compared with 4.07 in the control group. The authors proposed that the mechanism for such an effect may be due to the cardio-protective effects of omega-3 fatty acids and antioxidant vitamins found in abundance in the Mediterranean diet (324). The cardio-protective benefits were maintained up to 4 years after the first MI (325), with fewer cardiac deaths (326).

Two groups have studied the potential benefit of fish and fish oils in patients with pre-existing CVD. Firstly, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto miocario (GISSI-Prevenzione) trial reviewed the effects of fish oil supplementation in a post-MI cohort. A 20% reduction in overall mortality and a 45% reduction in sudden cardiac death was demonstrated on those on supplements (327). Secondly, the Diet and Reinfarction Trial (DART) studied patients for 2 years post MI and randomised them to either normal diet or a fish and fish oil supplemented diet (328).

However, a recently published study from The Netherlands assessed the effect of *n*-3 fatty acid supplementation in margarine versus placebo, given to early 5000 patients post-MI. There was no reduction in the primary end-point of rate of major CV events (329).

1.8.3.2 Effect of a Mediterranean-type diet on blood pressure

Several studies have examined the relationship between adherence to a Mediterranean-type diet and BP. The original Seven Countries Study gave a potential explanation for the lower CV mortality rates with lower levels of BP and lower BMI protecting against atherosclerosis (316). A significant reduction in systolic BP was noted in a Mediterranean-type diet study where either olive oil or mixed nuts were compared with a low-fat diet (mean reduction of 5.9mmHg and 7.1mmHg respectively and $p<0.001$ for both) (330). Alonso demonstrated that a high fruit and vegetable intake was inversely associated with BP levels (331).

In a converse design to usual Mediterranean diet studies, a research group in Italy assigned 57 normotensive volunteers to a 6-week intervention period of a 70% increase in energy from saturated fatty acids and decrease in carbohydrate

and mono-unsaturated fat. By the end of the intervention, systolic BP increased by 2.6mmHg in men ($p<0.05$) and by 4.8mmHg in women ($p<0.01$) when compared with the 2 week baseline period on their customary Mediterranean type diet. Diastolic BP did not significantly increase. After returning to their usual diet, BP readings reverted to baseline. The authors postulate that changes in the saturated fatty acid content of the diet has a significant impact on BP control (332).

1.8.3.3 Diabetes

Researchers have shown a reduced risk of diabetes with a 2-point increase in Mediterranean diet score (35% relative reduction, incidence rate ratio 0.65, 95% CI 0.44-0.95) (333). The metabolic syndrome describes a group of major risk factors for CVD such as dyslipidaemia, obesity, hypertension and diabetes (334). A reduced incidence of the metabolic syndrome has been demonstrated with a diet high in cereals and a high monounsaturated: saturated fat ratio (335). Karvounaris found no significant overall increase in metabolic syndrome prevalence in a cohort of 200 RA patients than in a group of 400 age and sex-matched controls (44% versus 41%, $p=0.5$) (336).

1.8.3.4 Potential mechanisms for cardiovascular benefits of a Mediterranean-type diet

The effects of dyslipidaemia are well-documented and a Mediterranean diet looks to have potential benefits on lipid profile with reductions in mean LDL-cholesterol (337), by as much as 11.3% in one study (338). In addition, reduced TC: HDL-cholesterol ratios have also been shown (330).

Endothelial dysfunction has been mooted as a possible early event in the evolution of atherogenesis as well as being a novel predictor of CVD risk. Improved endothelial function, as measured by FMD of the brachial artery has been demonstrated in a study of males with hypercholesterolaemia assigned to a Mediterranean diet (339). A significantly improved endothelial function score (a measure of BP and platelet aggregation) has been documented in patients assigned to a Mediterranean diet when compared to a control diet (340).

Finally, reduced markers of inflammation and coagulation (e.g. CRP, fibrinogen, IL-6 and homocysteine) have also been documented with adherence to such a

diet (341). Work from Kang and Leaf has demonstrated the electrical stabilization of cardiomyocytes by *n*-3 fatty acid which may go some way to explain the benefits of a high dietary fish intake (such as in a Mediterranean-type diet) or fish oil supplementation (342).

1.8.4 Mediterranean-type diet and inflammatory arthritis

1.8.4.1 Prevention of inflammatory arthritis

A number of associations between dietary intake and the development of inflammatory arthritis have been postulated. Researchers have shown the potential benefits of a Mediterranean-type diet in the prevention of RA. FFQ from 145 patients with RA were compared with those of 188 controls. The risk of developing RA was inversely and significantly associated with the consumption of cooked vegetables and olive oil (OR 0.38 and 0.24 respectively by multiple logistic regression analysis) (343).

UK epidemiologists based in Manchester proposed 2 similar theories. In the first, a lower intake of fruit, vegetables and vitamin C was associated with an increased risk of developing inflammatory arthritis (344). The second demonstrated that patients who consumed a high amount of red meat and protein were also at increased risk for developing inflammatory arthritis (345). A Mediterranean diet is naturally rich in fruit and vegetables and contains a lesser amount of red meat; therefore the work by Pattison and colleagues confirm the potential protective merits of adopting such a diet.

1.8.4.2 Improvement in inflammatory joint disease control

Swedish investigators conducted a study involving RA patients with established disease who strictly attended a hospital canteen for 2 meals per day (346). Twenty-six received a Cretan Mediterranean diet and 26 a control diet. The intervention group demonstrated a significant reduction in DAS28 by 0.56 ($p<0.001$) and in HAQ score by 0.15 ($p=0.02$), whereas the control group showed no benefit. Additionally, a study of a vegan diet, free of gluten, demonstrated a higher number of RA patients achieving an ACR 20% improvement in disease activity than patients in a control group (347).

1.8.4.3 Potential mechanisms for arthritis disease activity benefits of a Mediterranean-type diet

Oleocanthal, a compound found in olive oil, has been found to cause dose-dependent inhibition of COX1 and COX2 activities. This mimicry of the pharmacological benefits of ibuprofen may explain some of the health benefits listed in the sections above (348).

IL-6 is secreted by T cells and macrophages and is an important mediator of fever and acute phase response. It has an important role in the pathology of RA and as such, tocilizumab the first IL-6 receptor monoclonal antibody has been produced (349). Elevated plasma levels of IL-6 have been associated with a greater risk of CV and non-CV death in a cohort of elderly patients (350). Researchers have demonstrated that adherence to a Mediterranean-type diet was associated with a significant reduction in IL-6 (340) (341) (351) (352).

Fish oils have been proposed as potentially contributing to the health benefits of a Mediterranean-type diet (as documented in Sections 1.8.3.1-1.8.3.4) and this is especially pertinent to inflammatory control. *n*-3 (also known as omega-3) is a fatty unsaturated acid. It is derived mainly from ingested α-linolenic acid and eicosapentanoic acid from fish. Fish especially rich in *n*-3 include salmon, herring, mackerel, sardines and anchovies, and to a lesser extent, tuna. Another important source of *n*-3 is flax seeds (also known as linseed). This type of fatty acid has the capacity to modulate a number of inflammatory markers central to causing tissue damage; it has been shown to suppress IL-1ß (353), TNF (354), as well as ICAM-1 (355).

1.8.4.4 Potential role of fish and fish oils in rheumatoid arthritis

A double-blind placebo-controlled study randomised RA patients to 540mg γ-linolenic acid (in the form of evening primrose oil), 240mg fish oil (containing eicosapentaenoic acid) plus 450mg γ-linolenic acid or placebo. Results at 12 months demonstrated that those patients taking either fish oil or evening primrose oil managed to reduce their NSAID intake without any deterioration in disease activity (356). Sixty-six RA patients enrolled in a double-blind randomised placebo-controlled study were given either corn oil or fish oil in addition to diclofenac and the NSAID substituted for placebo at either week 18 or 22 while fish oil supplementation continued for another 8 weeks. Corn oil use

had no improvement in clinical parameters. Fish oil resulted in significant decrease in tender joint count and duration of EMS. There continued to be a significant reduction in tender joint count after diclofenac substitution (-7.8±2.6, p=0.011) (357). A double-blind placebo-controlled randomised trial assigned 97 patients with RA to either 10g of cod-liver oil containing 2.2g of *n*-3 essential fatty acids or an air-filled identical placebo capsules (358), 60% completed the study. 39% in the cod liver oil group and 10% in the placebo group managed to reduce their daily NSAID requirement by >30% (p=0.002) without deterioration in disease control. The authors postulate that supplements rich in *n*-3 could be used as NSAID sparing agents in RA patients.

Despite these positive results, and those published by others (359), relatively few patients with RA take fish oil supplements (360).The risk of developing RA is reduced by taking 2 or more fish meals per week compared with taking just one (adjusted OR 0.57, 95% CI 0.35-0.93) (361). This would again suggest a potential benefit of a Mediterranean type diet.

1.8.5 Mediterranean-type diet and weight

In subjects who were initially overweight at enrolment in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC) study, Mediterranean-diet adherence was associated with a significantly lower likelihood of becoming obese during the 3-year follow-up (318, 362). Adhering to a very low calorie diet results in both weight loss and a reduction in IL-6 levels, suggesting that circulating IL-6 levels may partly reflect adipose tissue production (363). A 2-year study was performed in over 300 moderately-obese patients assigned to 1 of 3 diets: low-fat and calorie-restricted, Mediterranean or low-carbohydrate with no calorie restriction. The most significant weight loss was seen with the latter 2 diets at 4.6kg and 5.5kg respectively in those who completed the 2 year intervention. The maximum weight loss was between months 1 and 6 and was also associated with increased dietary fibre (364). However, in studies focusing on the effect of a Mediterranean diet on RA, it has not been thought that weight loss contributed to an improvement in the joint disease – one may expect that weight reduction would lead to a reduction in mechanical stresses on joints in the lower limbs especially (365).

1.8.6 Other potential health benefits of a Mediterranean-type diet

1.8.6.1 Cancer

There is a significant evidence base suggesting that adherence to a Mediterranean-type diet may reduce cancer risk. For example, of over 65,000 females in the Etude Edpidémiologique auprès de femmes de l'Education Nationale arm of the EPIC (E3N-EPIC) cohort, 2381 cases of post-menopausal invasive breast cancer cases were identified over a median follow up period of 9.7 years. Adherence to a Mediterranean-type diet showed a negative association with breast cancer risk, especially oestrogen-positive and progesterone-negative (HR 0.85, 95% CI 0.75-0.95, p=0.003 for linear trend). A diet high in processed foods, fats and alcohol had a positive association with breast cancer risk (HR 1.20, 95% CI 1.03-1.38, p=0.007 for linear trend) (366).

The EPIC cohort had over 485,000 subjects, 30% of which were male, aged between 35 and 70 years in 10 European countries. An 18-unit relative adherence to a Mediterranean diet score was used to estimate adherence to diet type. A high score was associated with a significant reduction in gastric adenocarcinoma risk (HR 0.67, 95% CI 0.47-0.94). A 1 unit increase in this score was associated with a reduced risk of gastric adenocarcinoma of 5% (95% CI 0.91-0.99) (367).

1.8.6.2 Asthma and allergy

The link between diet, atopy (allergic hypersensitivity) and asthma control has been explored over recent years. In one study, 174 adult asthmatics were defined as controlled or non-controlled and dietary intake assessed by FFQ and subsequently Mediterranean diet score calculated (368). Controlled asthmatics (23% of total) had a significantly higher Mediterranean diet score than non-controlled asthmatics. The higher intake of fresh fruit decreased the probability of having non-controlled asthma (OR 0.29, 95% CI 0.10-0.83, p for trend=0.015). A cross-sectional survey of nearly 700 children aged 7-18 years living in rural Crete examined the relationship between diet, respiratory and allergic symptoms (369). 80% of children ate fresh fruit daily and 68% ate vegetables daily. A high level of adherence to a Mediterranean diet was protective for allergic rhinitis (OR 0.34, 95% CI 0.18-0.64). A high consumption of nuts, in

particular, was found to be inversely associated with wheezing (OR 2.19, 95% CI 0.20-0.98).

1.8.7 Problems with dietary studies

Clinical trials of dietary interventions are associated with a set of potential problems different from pharmaceutical drug trials. Recruitment can be much more difficult as the patients require undertaking some form of lifestyle modification, with associated impact on their day to day social activities. It is very difficult to monitor compliance in a dietary intervention study. Unfortunately, dropout numbers can be high in such clinical trials. A study investigating the effect of a particular diet cannot be performed in a double blind fashion. There are usually no direct commercial interests linked to a dietary study and consequently funding can be difficult.

1.9 SCOTTISH DIETARY POLICIES

Many aspects of social and economic policy impact on food consumption, diet and health. By the beginning of the 21st century, the Scottish diet was described as being not only worse than the closely neighbouring countries of England and Wales, but also worse than that of almost any other country in the Western world (370). Even today, many children are noted to be failing to eat enough fruit and vegetables and childhood obesity is rising. Sugar consumption is high with a subsequent legacy of dental disease. This is in spite of published evidence derived from the north Glasgow MONICA population surveys suggesting that there was increasing trends in the reported consumption of fruit and vegetables and oil-rich fish over the 10-year period 1986-1995 (371). A study of Scottish diet from the early 1990's as part of the Scottish Heart Health Study demonstrated that men and women in manual occupations had a poorer quality diet than those in non-manual occupations (306).

1.9.1 The James Report

In the early 1990s it was becoming increasingly apparent that the unhealthy Scottish diet was impacting on the wellbeing of the population. In 1992, the Chief Medical Officer for Scotland established a working group chaired by Professor Philip James to survey the diet of the Scottish people in a bid to assess

the relevance of diet to health and to make suggestions, if appropriate, for improvements and to assess their likely impact. "The Report on the Scottish Diet" was presented in 1993 and highlighted the need for a substantial change in Scotland's consumption of food and nutrients to bring about significant measurable population health benefits. The James Report (as it became known) heralded an important shift in public health policy (372).

1.9.2 The Scottish Dietary Action Group and subsequent health studies

The Scottish Diet Action Group (SDAG) was set up in 1994 with the task of preparing an action plan to meet the series of targets set out in the James Report of the previous year. National recommendations were outlined which included targets for dietary improvement in Scotland by the year 2005. The average intake of fruit, vegetables, wholemeal and brown breads, rice, pasta and oily fish needed to increase. It was vital that the average intake of salt, saturated fatty acids and sugar reduced significantly.

The traditional Mediterranean-type diet is consistent with the recommendations of the SDAG. Scottish nutritionists designed a 6-month study to evaluate the effectiveness of an internet-based tailored-feedback intervention promoting four key components of the Mediterranean diet (vegetables, fruit, legumes and monounsaturated: saturated fatty acid) (373). Those in the intervention group had significantly increased their consumption of the key components ($p= 0.002$, 0.025, 0.001 and <0.001 respectively). The authors reported that this intervention was easy to set up and implement with significant changes in participants eating habits.

The Scottish Health Survey of 2008 (374) demonstrated that there had been no significant increase in fruit and vegetable consumption between the surveys of 2003 and 2008. The average number of fruit or vegetable portions consumed per day was 3.4 for females and 3.1 for men. 24% of females and 20% of males consumed 5 or more portions per day. The percentage not consuming any fruit or vegetables per day was higher in the most deprived SIMD quintile compared with the least (19% versus 4%). Alcohol consumption was also higher in the most deprived group with 11% consuming more than 50 units per week (compared with 5% in the least deprived group).

1.9.3 Health Promotion within NHS Greater Glasgow & Clyde

Greater Glasgow Health Board was created in 1974 and became NHS Greater Glasgow in 2003. In 2006 it was renamed NHS Greater Glasgow and Clyde. The Health Promotion Department embarked on playing a leading role in improving health for all those living in the area, by working in active partnership with individuals, communities and organisations. They describe two main aims; firstly, to enable those who live (or work) in Glasgow to improve their health and that of the local population and secondly, to reduce inequalities in health in Glasgow. The remit of the nutrition team includes: to increase awareness of what constitutes a healthy diet and to increase access to information and services related to food. The affordability and availability of healthy food for all is paramount.

1.10 SOCIAL DEPRIVATION

1.10.1 Townsend Index

The Townsend Index was derived in 1988 to provide a measure of deprivation and disadvantage in England (375). Four variables (unemployment, non-car ownership, non-home ownership and household overcrowding) combine to form an overall score. The higher the Townsend Index score, the more deprived and disadvantaged an area is thought to be. Different areas can be ranked in relation to one another.

1.10.2 Carstairs Index

The Carstairs Index is an score of deprivation to identify socio-economic confounding (376). It was developed for Scotland as an alternative to the Townsend Index based upon the 1981 census data. It is based upon 4 census indicators: low social class (class 4 or 5), lack of car ownership, overcrowding and male unemployment. Areas are then split by postcode. A composite score is created and the deprivation score divided into 7 separate categories ranging from very high (category 6 and 7) to very low deprivation (category 1 and 2). Scores were recalculated in 1991 using more up to date census information.

1.10.3 Scottish Index of Multiple Deprivation

SIMD has recently been adopted as a tool by the Scottish Government, local authorities, the NHS and government bodies (377). It combines 37 indicators across 7 domains (current income; employment; health; education, skills and training; housing; geographic access and crime). The driving principle behind this index is to target government action to the areas of greatest need by identifying small area concentrations of multiple deprivations across Scotland. SIMD scores range from 0.54 (least deprived) to 87.60 (most deprived) and scores can be divided into quintiles of least to most deprived, as detailed in Table 1.17.

Table 1.17 – SIMD quintiles

Population fifth	SIMD range
1st	0.54-7.63
2nd	7.64-13.49
3rd	13.50-21.16
4th	21.17-33.93
5th	33.94-87.60

Where 1st quintile is the least deprived and 5th quintile is the most deprived

Adapted from (377)

1.10.4 Rheumatoid arthritis and social deprivation

Evidence suggests that social deprivation associates with poor outcome in RA. For instance, a cohort of 200 RA patients in the West of Scotland recruited to a DMARD study was followed prospectively for 12 years (378). 47.5% of patients died in the follow up period, with 57% dying from a cardiorespiratory cause and 21% from a neoplasm. The median age of death was lower and the percentage of deaths higher in the most deprived patients (Carstairs groups 6 and 7). This Carstairs grouping had a 1.66 times greater mortality than the least deprived

group, Carstairs 1 and 2 (95% CI 0.74-3.69). It is thought that some of this excess risk may be due to cigarette smoking. Another study from the West of Scotland confirmed poorer function and increased medical need in a 5 year follow up of over 400 patients with RA (379). Similar finding of a worse clinical course in nearly 900 English patients with RA has been reported (380).

1.10.5 Cardiovascular disease and social deprivation

CHD has been found to be associated with socioeconomic deprivation across the world (381). O'Flaherty et al found that the overall age adjusted CHD mortality in the over 35s between 1986 and 2006 had decreased (by 61% in men and 56% in women) (382). However they determined that the rate of decline of mortality was slowing down in young women more so than in young men. Up to a 6-fold differential in CHD mortality was apparent between least and most deprived areas; this difference disappeared in the over 85 year old group.

1.11 POTENTIAL MODIFICATION AND FURTHER ASSESSMENT OF CARDIOVASCULAR RISK IN RHEUAMTOID ARTHRITIS

1.11.1 Hypothesis under investigation

In this thesis I aim to explore the effect of novel interventions on various aspects of RA. Specifically I will investigate the feasibility and effect of anti-inflammatory withdrawal in patients with well-controlled RA as well as the impact of a Mediterranean-type diet on disease activity within the Glasgow RA population. Finally, given recent evidence linking social deprivation with CV risk as well as poor RA outcomes, this will be explored further by comparing outcome in an RA cohort according to conventional and new CV risk algorithms.

The rationale to the NSAID withdrawal study was that removal of this therapy plus any required active intervention would provide equivalent symptom control to that achieved by continuing NSAID as assessed by DAS, pain score and functional assessments. The Mediterranean-diet study was set up to assess if existing resources could be used as much as possible.

1.11.2 Aims of investigations

1. To assess the tolerability and impact of NSAID withdrawal from a group of RA patients with low disease activity – the primary outcome being DAS44, secondary outcomes being effect on BP, GI symptoms and renal function.

2. To explore the feasibility and acceptability of introducing a Mediterranean-type diet in females with RA, predominantly from areas of social deprivation in Glasgow. Additionally, to assess the impact of such a dietary intervention on disease activity, CV parameters and haematological markers.

3. To examine the impact of social deprivation on cardiovascular risk scores using the Mediterranean-diet cohort, and compare the outcome of using a newer CV risk score (ASSIGN) with traditional scores (Framingham and JBSCRP).

CHAPTER 2

Patients and Methods

2.1 SUMMARY

This chapter provides a description of the general protocols and the clinical techniques used in the studies detailed in this thesis.

2.2 ETHICAL GUIDANCE AND APPROVAL

Approval for both the NSAID withdrawal study and the Mediterranean-type diet study was granted by the Local Research Ethics Committee (LREC) at Glasgow Royal Infirmary. All patients gave written informed consent after having 24 hours to review the Patient Information Sheet before making a decision.

All research using samples from controls and patients was in accordance with the World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, most recently amended by the 59th WMA General Assembly in Seoul, October 2008 (383).

2.3 PATIENT RECRUITMENT

2.3.1 Non-steroidal anti-inflammatory drug withdrawal study

Patients were recruited from clinics of 2 Consultant Rheumatologists at Glasgow Royal Infirmary. Suitable patients were either identified during the clinic consultation or approached staff themselves after viewing a recruitment poster (Appendix II) in the clinic waiting area. If thought appropriate they were invited to take part in the study and were provided with a Patient Information Sheet (Appendix III). Potential recruits were telephoned at home to invite them to a baseline assessment if they wished to proceed with study involvement. Inclusion and exclusion criteria are detailed in Sections 3.2.1 and 3.2.2. All patients gave written informed consent (Appendix IV).

2.3.2 Mediterranean-type diet study

Female patients with RA were recruited over a nine month period. Three hospital sites in Glasgow were used: Royal Infirmary, Southern General and Stobhill Hospital. These sites were chosen with the aim of recruiting patients from within one of the Social Inclusion Partnership areas in Glasgow, these are

areas of social deprivation (384) (385). Suitable patients were either identified during the clinic consultation or from within multi-disciplinary team discussions. If thought appropriate they were invited to take part in the study and were provided with a Patient Information Sheet (Appendix V). Potential recruits were telephoned at home to invite them to a baseline assessment if they wished to proceed with study involvement. Inclusion and exclusion criteria are detailed in Sections 4.2.1 and 4.2.2. All patients gave written informed consent (Appendix VI).

2.4 ASSESSMENT OF DISEASE ACTIVITY

The relationship between joint swelling and tenderness can vary from person to person and at different time points. It has become accepted practice to assess both swelling and tenderness when examining a patient with inflammatory arthritis (386). Methods have changed of evaluating disease activity with variations in: number of joints assessed, which joints are assessed and scoring system (e.g. graded scale or abnormal versus normal).

DAS has become the preferred combined index to include clinical and laboratory parameters. DAS dates back to 1983 when a small clinical trial modified an existing disease activity index. This allowed classification into either high or low disease activity and included the views of both patient and doctor (387). Further work developed the DAS to cover a number of variables to discriminate between different levels of disease activity (388).

Thus the commonly used DAS is a statistically derived index combining tender joints, swollen joints, ESR (or CRP) and patient GH (389). DAS values are continuous, normally distributed and are well validated in clinical trials. The component parts to the DAS are described below. Tenderness and swelling are assessed separately in each joint. Tenderness is more sensitive to change and correlates with pain, while swelling correlates with acute phase reactants and radiographic progression. Tender and swollen joint count contributes numerically to approximately 50% of the DAS.

Common to both DAS44 and DAS28 is the patient's assessment of GH. It is measured on a 100mm visual analogue scale (VAS) (r=0.995, random

measurement error=0.12). This is a reliable and reproducible method of following the course of pain and disability (390). While a pain score is not part of the formal calculation of either DAS44 or DAS28, it can be helpful as part of a general assessment of the patient and monitoring of a therapeutic intervention. Pain score is graded on a VAS from 0-100mm.

2.4.1 Disease Activity Score-44

DAS based on 44-joint count for swelling is known as the DAS44 or "original" DAS. It gives a numerical score on a scale from 1-9. It is calculated using a mathematical formula detailed in Table 2.1, when 4 components are available: Ritchie Articular Index (RAI), 44-swollen joint count, ESR (or CRP) and patient GH score.

When global disease activity assessment is not available, a 3 component DAS can be calculated using an alternative formula, also detailed in Table 2.1.

While the 28-joint count is the basis for deciding on possible escalation of therapy to anti-TNF (14), in daily clinical practice a joint count which includes the feet joints (such as the DAS44) is felt better by some clinicians to follow the course of the disease of individual patients.

DAS44 was used in the non-steroidal withdrawal study, described in Chapter 2, to better capture changes in a larger number of joints than using DAS28 would allow.

Table 2.1 - Equations for calculating 44-joint disease activity score (DAS44)

Equations for calculating DAS44
4 components (ESR):
DAS44 = 0.53938√(RAI)+ 0.06465(SW44)+0.33Ln(ESR)+0.00722(GH)
4 components (CRP):
DAS44 = 0.53938√(RAI)+ 0.06465(SW44)+0.17Ln(CRP+1)+0.00722(GH)+0.45
3 components (ESR):
DAS44= 0.53938√(RAI)+ 0.06465(SW44)+0.33Ln(ESR)+0.224
3 components (CRP):
DAS44= 0.53938√(RAI)+ 0.06465(SW44)+0.17Ln(CRP+1)+0.65

Where: RAI= Ritchie Articular Index (53 joints in 26 "units" or "blocks", graded for tenderness), SW44= 44 joint count for swelling, LnESR= natural logarithm of Westergren's erythrocyte sedimentation rate (mm/hour) and GH= global health (or patients' global assessment of disease activity) on a visual analogue scale of 100mm.

Adapted from (389) (391)

2.4.1.1 Ritchie Articular Index

The RAI grades tenderness in 53 joints including the feet (389) (392). The method is sensitive to detect even small changes in joint tenderness. The reproducibility when used by one observer is satisfactory, but the inter-observer variation can be higher. All 53 joints included in the RAI are assessed separately. However the MCP and PIP joints of each hand, MTP joints of each foot, temperomandibular joints, sternoclavicular joints and acromioclavicular joints are calculated as a single unit – the highest score for a single joint gives the score for the unit. The joints are graded for tenderness on a 0-3 scale defined as: (0) no tenderness, (1) pain on pressure, (2) pain and winced and (3) winced

and withdrew. Pressure to elicit tenderness is exerted by the examiner's thumb and index finger (at a sufficient pressure to cause "whitening" of the examiners' nail beds). The 53 joints involved are detailed in Table 2.2.

2.4.1.2 44-swollen joint index

When a synovial effusion is present the joint is invariably swollen. Joint swelling is detectable along the joint margins and fluctuation is a characteristic feature. Joint swelling may influence the range of joint movement. Bony swelling, deformity and oedema surrounding the joints do not constitute joint swelling for the purposes of this score.

All joints are assessed separately. The joints are scored for swelling on a 0-1 scale: (0) no swelling and (1) swelling. The individual joint scores are summed. The 44-swollen joint count is assessed in the same joints as the RAI, with the exclusion of 9 joints in which swelling is difficult to detect: temperomandibular joints, cervical spine, hips, subtalar joints and midtarsal joints. The 44 joints involved are detailed in Table 2.2.

Table 2.2 - A comparison of the joints included in DAS44 for pain (Ritchie Articular Index) and swelling (44-swollen joint count)

Joints included	
Ritchie Articular Index	**44-swollen joint count**
10 PIP joints	10 PIP joints
10 MCP joints	10 MCP joints
2 wrist joints	2 wrist joints
2 elbow joints	2 elbow joints
2 glenohumeral joints	2 glenohumeral joints
2 acromioclavicular joints	2 acromioclavicular joints
2 sternoclavicular joints	2 sternoclavicular joints
2 temperomandibular joints	2 knee joints
Cervical spine	2 ankle joints
2 hip joints	10 MTP joints
2 knee joints	
2 ankle joints	
2 subtalar joints	
2 midtarsal joints	
10 MTP joints	

Note: The cervical spine and hip joints are not examined directly for joint tenderness; the patient is asked if they have pain in the posterior cervical spine or pain in the groin on hip movement.

Adapted from (389)

2.4.2 Disease Activity Score-28

The DAS28 is based on tenderness and swelling in 28 joints and each feature is assessed separately in each of the joints (389) (393). Joints are scored for swelling on a 0-1 scale: (0) no swelling and (1) swelling. Joints are scored for tenderness on a 0-1 scale: (0) no tenderness and (1) tenderness. The 28 joints comprising this index are detailed in Table 2.3. DAS28 was used in the Mediterranean-type diet study described in Chapter 4 to allow a more rapid follow up of a greater number of patients.

Table 2.3 - The 28 joints assessed for swelling and tenderness in DAS28

Joints involved - Tender and swollen joint count
10 PIP joints
10 MCP joints
2 wrist joints
2 elbow joints
2 glenohumeral joints
2 knee joints

Adapted from (389)

DAS28 based on 28-joint count for swelling and tenderness, in addition to ESR (or CRP) and patient GH score is calculated using a mathematical formula detailed in Table 2.4. Where patient GH score is not available, a 3 component DAS28 can be calculated using an alternative formula, also detailed in Table 2.4. It gives a numerical score on a scale from 0.49-9.07.

Table 2.4 - Equations for calculating 28-joint disease activity score (DAS28)

Equations for calculating DAS28
4 components (ESR):
DAS28 = 0.56 √(TEN28)+0.28√(SW28)+0.70Ln(ESR)+0.014(GH)
4 components (CRP):
DAS28 = 0.56 √(TEN28)+0.28√(SW28)+0.36Ln(CRP+1)+0.014(GH)+0.96
3 components (ESR):
DAS28 = [0.56 √(TEN28)+0.28√(SW28)+0.70Ln(ESR)]+0.16
3 components (CRP):
DAS28 = [0.56 √(TEN28)+0.28√(SW28)+0.36Ln(CRP+1)]x1.10+1.15
Approximate conversion from DAS44:
DAS28= 1.072(DAS44)+0.938

Where TEN28= 28 joint count for tenderness, SW28= 28 joint count for swelling, LnESR=natural logarithm of Westergren's erythrocyte sedimentation rate (mm/hour) and GH=global health (or patients' global assessment of disease activity) on a visual analogue scale of 100mm.

Adapted from (389) (391)

2.4.3 Comparison of DAS44 and DAS28

The 2 commonly used disease activity scores differ in which joints are assessed (Table 2.2 and Table 2.3) and also in their numerical outcome. The DAS44 with its more comprehensive joint count is not interchangeable with the DAS28. The DAS28 gives higher values than the original DAS. An approximate DAS28 can be converted from DAS44 by an additional formula detailed in table 2.4. Different numerical ranges are used for DAS44 and DAS28 to define the level of disease activity exhibited, as detailed in Table 2.5.

Table 2.5 – Comparison of disease activity 'criteria' between DAS44 and DAS28

	DAS44	DAS28
High disease activity	>3.6	>5.1
Moderate disease activity	2.4-3.6	3.2-5.1
Low disease activity	1.6-2.4	2.6-3.2
Remission	<1.6	<2.6

Adapted from (17) (21)

2.5 FUNCTIONAL ASSESSSMENTS

Functional assessments are frequently used in research but used less often in clinical practice (394), except as part of the assessment for suitability for biologic therapy (14).

2.5.1 Short Form 12-item

The short form 12-item study (SF-12) was designed to measure general health status from the patient's point of view. It is based upon the more in-depth SF-36, which is the most widely evaluated generic patient assessed health outcome measure (395) (396). It is a quick survey for the patient to complete with most finding that it only takes a few minutes to perform. The SF-12 includes 8 health concepts or "domains" commonly represented in health surveys and also featured in the SF-36. One or 2 questions cover each of these domains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health.

Results are expressed in terms of 2 meta-scores: the physical component summary (PCS) and the mental component summary (MCS). A high score

indicates better functioning. Test items are scored and normalised in an algorithm via a computer program (397). Both PCS and MCS were designed to have a mean score of 50 and a standard deviation of 10 in a representative sample of the population of the USA; therefore scores of over 50 represent above average health status. PCS scores are expected to decline with age more than MCS scores would. A sample of the SF-12 form patients completed in the NSAID withdrawal study is documented in Appendix VII.

2.5.2 Health Assessment Questionnaire

The HAQ originated in the late 1970s from Rheumatologists in the USA (398) (399). It was one of the first self-reported functional disability measures. The most commonly used version is the "short" or "2-page" HAQ which is completed by the patient. It rates the degree of difficulty experienced with everyday tasks and takes account of the need for adaptations and help from carers. It contains the HAQ disability index, visual analogue pain scale and patient GH scale. It does not capture disability associated with sensory organ dysfunction or psychological dysfunction. A sample of the HAQ form patients completed in the Mediterranean-type diet study is documented in Appendix VIII.

2.5.3 Comparison of SF-12 and HAQ

HAQ is a quick guide to identifying problems with activities of daily living but is not very sensitive to change. The SF12 is less valuable than HAQ in reviewing problems with activities of daily living but is more sensitive to change in physical function over time (400).

2.6 INDICES OF SOCIAL DEPRIVATION

A number of different indices are used in the UK. These include the Carstairs Index, the Townsend Index and SIMD. All analyse patterns of deprivation across geographical areas. In Sections 2.6.1 and 2.6.2 below, the indices used within the studies included in this work are discussed.

2.6.1 The Carstairs Index

The Carstairs Index is an score of deprivation to identify socio-economic confounding (376). It was developed for Scotland as an alternative to the Townsend Index based upon the 1981 census data. It is based upon 4 census indicators: low social class (class 4 or 5), lack of car ownership, overcrowding and male unemployment. Areas are then split by postcode. A composite score is created and the deprivation score divided into 7 separate categories ranging from very high (category 6 and 7) to very low deprivation (category 1 and 2). Scores were recalculated in 1991 using more up to date census information.

2.6.2 Scottish Index of Multiple Deprivation

SIMD has recently been adopted as a tool by the Scottish Government, local authorities, the NHS and government bodies (377). It combines 37 indicators across 7 domains (current income; employment; health; education, skills and training; housing; geographic access and crime). The driving principle behind this index is to target government action to the areas of greatest need by identifying small area concentrations of multiple deprivations across Scotland. SIMD scores range from 0.54 (least deprived) to 87.60 (most deprived) and scores can be divided into quintiles of least to most deprived as illustrated previously in Table 1.15.

Information regarding SIMD was calculated using the postcode from the patient address given at study commencement and displayed as part of the ASSIGN score calculator (401).

2.7 BLOOD SAMPLES

Peripheral venous blood was drawn into Vacutainer® tubes and analysed as per individual study protocol detailed in sections 2.7.1 and 2.7.2 below.

2.7.1 Non-steroidal anti-inflammatory drug withdrawal study

A clot-activated blood sample was sent to the clinical biochemistry laboratory of Glasgow Royal Infirmary for measurement of CRP, lipid profile and urea and electrolytes via the routine service. eGFR has become a standard method of estimating renal function and forms the basis of chronic kidney disease staging

(402). Normal eGFR is approximately 100 ml/min/1.73m^2. In this study, eGFR was calculated for each individual patient at the 3 time-points using the abbreviated modification of diet in renal disease (MDRD) equation:

$$\textbf{eGFR}\ (\text{ml/min/1.73m}^2) =$$

$$186 \times (\text{creatinine} / 88.4)^{-1.154} \times (\text{age})^{-0.203}\ (\times 0.743 \text{ if female})$$

An additional multiplication factor of 1.210 did not have to be used in this cohort as all patients were white (403).

An ethylenediaminetetraacetic acid (EDTA) sample was sent to the clinical haematology laboratory of Glasgow Royal Infirmary for measurement of ESR by the Westergren method via the routine service.

2.7.2 Mediterranean-type diet study

A clot-activated blood sample was sent to the clinical biochemistry laboratory of the hospital where the patient was being assessed (either Glasgow Royal Infirmary, Southern General Hospital or Stobhill Hospital) for measurement of CRP, lipid profile and urea and electrolytes via the routine service. An EDTA sample was sent to the clinical haematology laboratory of the hospital for measurement of ESR by the Westergren method via the routine service.

2.8 FOOD FREQUENCY QUESTIONNAIRES

No dietary assessment method is faultless. The FFQ was used in the Mediterranean-type diet study on the advice of the University of Glasgow Human Nutrition Departments to give, what is at best, an approximation food intake of the study participant. The FFQ is a validated questionnaire originally developed to assess total intake of energy and macronutrients (protein, fat and carbohydrate) at a time when antioxidants were not a focus of interest. Many variations do exist (311).

2.8.1 Benefits of the food frequency questionnaire

FFQ can be used in a variety of research settings: cross-sectional or surveillance, case control (retrospective), cohort (prospective) or in an intervention study. The individual's usual intake is documented and information on total diet obtained. There are low investigator costs and the administration of such a questionnaire tends not to affect the patient's eating behaviour (404).

2.8.2 Drawbacks of the food frequency questionnaire

Use of the FFQ is associated with an amount of measurement error, due to the limitation in its ability to estimate usual intake accurately. There can be problems with administering an paper-based FFQ in patients with poor vision or cognitive difficulties. A specific FFQ designed for use in a general population may be suboptimal in a patient with ethnic eating patterns. The estimation of portion size can be difficult for a patient and many FFQ designs have attempted to address this issue. FFQ generally include more than 100 individual line items and as such can take 30-60 minutes to complete – this raises concerns about the reliability of responses and response rates (404).

2.8.3 Analysis of the food frequency questionnaire in the Mediterranean-type diet study

A sample page of the FFQ (incorporating drink and fruit intake only) is included in Appendix I; due to limitation of space in this manuscript a full questionnaire is not included. Additional questions about fruit intake were included in the adapted FFQ for this study. These questions were analysed separately using the Diet5 computer package and the nutrient data added to the data estimated by DietQ to calculate the daily intake of vitamins A, C and E. Questionnaires were analysed by students in the Human Nutrition Department of the University of Glasgow. The computer packages apply different weightings to the answers of different questions, meaning that analysis of a completed paper version of the FFQ is not as straight-forward as one might assume. The main elements extracted from the FFQ for this study were: (a) fruit, vegetable and legume consumption, (b) Vitamin A, C and E intake, (c) monounsaturated fat consumption and (d) saturated fat consumption.

2.9 STATISTICAL ANALYSIS

The variables from each data-set (outlined in Chapter 3, 4 and 5) did not follow normal distribution and therefore non-parametric tests were used.

Wilcoxon signed-rank test is a non-parametric statistical hypothesis test used to compare two related samples to assess if their population mean ranks differ (i.e. a paired difference test). Additionally this test can be used as an alternative to the paired Student's t-test when the population cannot be assumed to be normally distributed or the data is on the ordinal scale. This test was used for comparing results within the same treatment group.

The Mann-Whitney U test is also known as the Mann-Whitney-Wilcoxon or Wilcoxon rank-sum test. It is also a non-parametric statistical hypothesis test for assessing whether one of two samples of independent observations tends to have larger values than the other, i.e. comparing results between intervention groups.

A result is of statistical significance if it is unlikely to have occurred purely by chance. The amount of evidence required to accept that an event is unlikely to have arisen by chance is known as the p-value or the significance level. Choosing a level of significance has previously been thought of as arbitrary; for many applications a level of 5% (=0.05) is chosen.

Statistical Package for the Social Science (SPSS) version 15 was used throughout.

CHAPTER 3

A Pilot Study of Non-Steroidal Anti-Inflammatory Drug Withdrawal in Patients with Stable Rheumatoid Arthritis

3.1 INTRODUCTION

DMARD are now introduced early in modern management of RA to reduce disease activity and disease progression. Many patients continue to take anti-inflammatory drug therapy regularly, despite good control of their arthritis while taking DMARD. Given the controversies and debate surrounding the CV and GI safety of NSAID and COX2 inhibitors, a study was designed around the withdrawal of these drugs in a specific group of patients with RA attending Glasgow Royal Infirmary's Rheumatology out-patient department.

The objective of this study was to assess the feasibility and acceptability of an abrupt cessation of anti-inflammatory drugs while maintaining good symptom control, if necessary by undertaking a program of alternative alleviate symptoms and if necessary introduce additional therapies.

3.2 JUSTIFICATION OF STUDY DESIGN AND PROTOCOL

The rationale to this study was that the withdrawal of NSAID plus any required active intervention would provide equivalent symptom control to that achieved by continuing NSAID as assessed by DAS, pain score and functional assessments. The primary outcome of this study was the effect on DAS following NSAID withdrawal at 12 weeks. Secondary outcomes were the effects on BP, GI symptoms and renal function at 12 weeks.

As this was an open labelled observational feasibility study, no specific power calculations were performed. It was felt that a sample size of 30 would be large enough to provide helpful results, but small enough to allow rapid and comprehensive follow-up. This would facilitate evaluation of either a future larger study or rolling-out NSAID withdrawal in a mainstream clinical setting.

Our initial study design had been to randomise patients on NSAID to either continuing this therapy or switching to placebo. We concluded that obtaining matching placebo tablets would be difficult given the many different NSAID preparations used by patients. Thus, the study design was changed to an open label pilot of NSAID withdrawal in all participants. Had we found that we were unable to recruit the required number of participants or if a large number of

study participants were unable to adhere to the study protocol, the pilot study would have been terminated.

3.2.1 Inclusion criteria

Patients aged 18 years or older were considered for inclusion if they: (a) had a greater than 6 month history of RA (diagnosis made by a Consultant Rheumatologist), (b) had been seropositive for RF at some point in their disease course, (c) had good control of the inflammatory component of their RA, as demonstrated by a DAS44 ≤2.8, (d) NSAID therapy on ≥25 out of 30 days in an average month, (e) were on a stable DMARD dose for ≥1 month and (f) if prescribed prednisolone, taking ≤10mg per day. RF was chosen as an inclusion criteria as ACPA was not routinely being tested for in our department at time of study recruitment.

To recap section 2.3.1, patients were recruited from clinics of 2 Consultant Rheumatologists at Glasgow Royal Infirmary. Suitable patients were either identified during the clinic consultation or approached staff themselves after viewing a recruitment poster (documented in Appendix II) in the clinic waiting area. If thought suitable they were invited to take part in the study and were provided with a Patient Information Sheet (Appendix III). Potential recruits were telephoned at home to invite them to a baseline assessment if they wished to proceed with study involvement. The study was approved by the LREC and patients gave written informed consent (Appendix IV).

The original protocol which was put forward did not specify a DAS44 level in the inclusion or exclusion criteria. The inclusion criteria was modified to include a DAS44 of ≤2.8 after discussion with the LREC; the Committee were concerned that withdrawing NSAID from patients with a higher disease activity level may have been detrimental to their disease control and hence led to unacceptable adverse effect on quality of life. A DAS44 of ≤2.8 falls within the range for 'moderate' disease activity, as previously illustrated in Table 2.5.

3.2.2 Exclusion criteria

Inability to give written informed consent resulted in exclusion of participation. Patients with a planned operative intervention during the duration of the study were disqualified since it was anticipated that increased use of analgesia, for reasons other than inflammatory joint symptoms, may have occurred. Patients were excluded if specific concurrent medical problems were present that may have influenced the assessment of disease activity by causing an increase in analgesia requirements: viz fibromyalgia, severe osteoarthritis, dysmenorrhoea and menorrhagia.

3.3 SAFETY AND MEDICATION DOCUMENTATION

3.3.1 Safety

Any adverse event, including the onset of a new illness and the exacerbation of pre-existing conditions were reported and documented in study notes and in medical case records: nature of event, start and stop dates, severity, relationship to intervention and outcome. Any serious adverse event such as death, life-threatening adverse event or significant disability or incapacity was to be notified to the Chief Investigator within 24 hours. This would then be discussed with the local Ethics team. Planned surgery or hospitalisation, agreed upon before inclusion in the study, was not classified as a serious adverse event.

We followed the local recommendations for increasing doses and monitoring of DMARD therapy. Significantly abnormal laboratory value(s), which are seen on occasion with standard DMARD dose escalation, were documented and acted upon as clinically appropriate. Possible interventions included DMARD dose reduction, DMARD being withheld for a period of time and withdrawal of therapy altogether.

3.3.2 Medication documentation

At baseline, the patient's full list of prescribed medications and any other supplements was documented. They were then asked to stop taking their prescribed NSAID. This was an abrupt cessation of treatment; no tapering of dose was advised. The patient's GP was contacted by letter to confirm the

above intervention and asked not to prescribe NSAID for the duration of the 12-week study period. The patients themselves were asked not to purchase or take over-the-counter NSAID from a pharmacy; this was made clear in the Patient Information Sheet. They were reviewed at 6 and 12 weeks and were able to make telephone contact with the study physician or nurse for further advice if required between visits. A formal additional review could be undertaken if appropriate. Patients were continued on all pre-existing DMARD, anti-TNF, analgesic medication plus any established prednisolone therapy.

3.3.3 Escalation of analgesia and DMARD therapy

The regimen for escalation of other therapies, if required for increase in RA disease activity or increase in pain, was as noted below:

Step 1

Increase of a peripherally acting or codeine-based analgesic to a maximum tolerated dose (paracetamol could be used in combination with dihydrocodeine or tramadol, compound agents such as co-codamol could only be used individually):

- Paracetamol 1g - 4 times daily
- Co-Codamol 8/500 - 8 tablets daily
- Co-Codamol 30/500 - 8 tablets daily
- Co-Dydramol 10/500 - 8 tablets daily
- Dihydrocodeine 30-60mg - 4 times daily
- Tramadol 50-100mg - 4 times daily

Step 2

Corticosteroids could be given by one of two routes; IM injection for a generalised flare, e.g. 80mg of triamcinolone acetonide (Kenalog®), or IA injection of a symptomatic swollen joint unless it had been injected in the previous 3 months, e.g. 5-40mg of triamcinolone acetonide: the choice of dose depended on the size of the inflamed joint. The method of corticosteroid administration was discussed between physician and patient. A maximum of 3 joints could be injected per visit, to a maximum total dose of 120mg triamcinolone acetonide.

Step 3

Depending on the initial therapy, DMARD therapy was optimised as outlined:

- Methotrexate – increments of 2.5mg per week at monthly intervals to a maximum dose of 25mg per week
- Sulfasalazine – increments of 500mg weekly to a maximum daily dose of ≤4g
- Sodium aurothiomalate (myocrisin) – increase frequency to a maximum dose of 50mg per week
- Leflunomide – maximum daily dose 20mg
- Hydroxychloroquine – maximum daily dose 400mg

Those who failed on mono-DMARD therapy would be offered combinations of DMARDs which have been shown to be of benefit in clinical studies (12).

3.4 STUDY ASSESSMENTS

3.4.1 General

Patients were seen at the Centre for Rheumatic Diseases at Glasgow Royal Infirmary by the study physician and Rheumatology Nurse Specialist acting as metrologist. The study duration was 12 weeks with clinical and laboratory assessments made at 0, 6 and 12 weeks. Patients were given the option of contacting the study team at any point for advice and given the opportunity to drop-out at any time.

At the baseline assessment written informed consent was obtained from the patient if entry criteria were met. Current medication, relevant past medical history, alcohol consumption and smoking status were documented. DAS44 was calculated on the basis of RAI, swollen joint count, patient global assessment (VAS / 100mm) and ESR, as detailed in Section 2.4.1. BP, height, weight, ESR and renal function were recorded. Additionally, SF-12 questionnaire was completed (as detailed in Section 2.5.1).

At 6 and 12-week assessments the following measurements were recorded: SF-12 questionnaire, DAS44, ESR, renal function, BP and updated medication list. The patients' analgesia diary, completed over the preceding 6 weeks was

reviewed. Intervention as deemed necessary could be performed at this stage (IM or IA steroid injection, escalation of analgesia and / or alteration of DMARD therapy).

3.4.2 Blood pressure recordings

An *A&D* digital BP monitor (model UA-767) was utilised throughout the study; this was a BHS approved monitor. A standard adult cuff (size 22-32cm) was used along with this. The BHS guidelines for the measurement of BP using an digital monitor were followed (405) (406). Firstly, the patient was seated in a quiet room for at least 5 minutes; relaxed, not speaking or moving. The patient's arm was supported at the level of the heart and any tight clothing constricting the arm was removed. The BP cuff was placed around the patient's upper arm with the indicator mark on the cuff over the brachial artery – the bladder encircling at least 80% of the arm but not exceeding more than 100%. At the baseline visit, BP was tested in both arms. The arm with the highest reading was recorded. That arm was then used in all subsequent measurements for the patient. BP monitoring was repeated 3 times and the average of the 3 readings documented.

3.4.3 Other documentation

BMI, defined as weight (kg) divided by the square of height (m^2) was recorded.

Upper GI symptoms over the preceding 6 weeks were documented as: (a) nil, (b) occasional, (c) regular or (d) daily.

Average alcohol intake was documented as: (a) nil, (b) 1-10 units per week, (c) 11-20 units per week or (d) >21 units per week.

Current dietary olive oil use and supplementary fish oil use was documented.

Two descriptive scores of deprivation were calculated and documented for each participant: Carstairs Index (376) and SIMD (377) (407). Deprivation was documented in part to assess whether this contributed to any difference in CV risk factors.

3.5 STATISTICAL METHODS

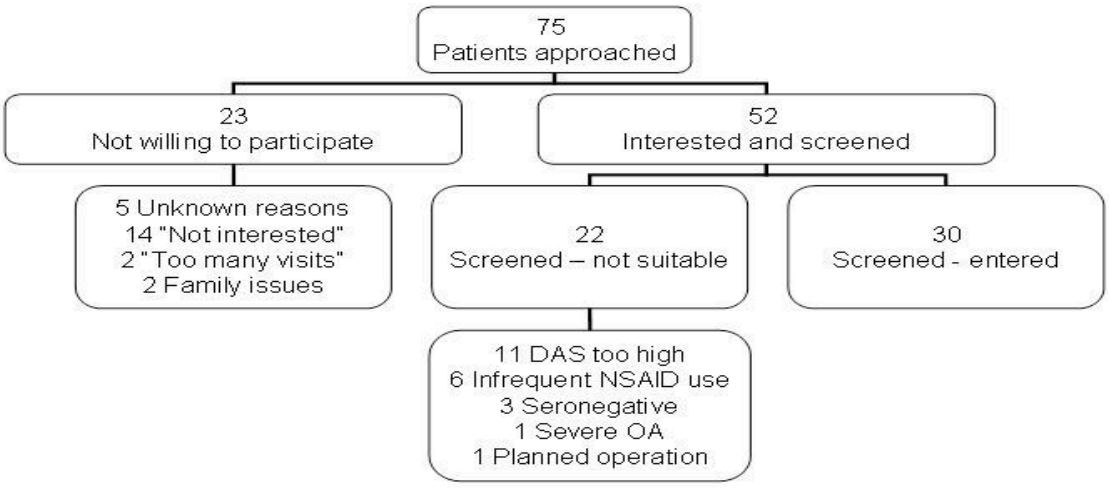
SPSS version 15.0 software was used for statistical analysis. As outlined in Section 3.2, no specific power calculations were carried out. Wilcoxon signed-rank test was used as a non-parametric hypothesis test to compare two related results (e.g. baseline and 6 weeks, baseline and 12 weeks, 6 and 12 weeks) to assess whether their mean ranks differed. Statistical significance was set as a p-value of <0.05 (see also Section 2.9 for additional statistical information).

3.6 RESULTS

3.6.1 Patient recruitment

Seventy-five patients expressed an initial interest in participating in the study or were approached by medical staff. Twenty-three were not willing to participate for reasons which included subsequent loss of interest in the study and difficulties coming up to the hospital unit for the study visits. Twenty-two did not meet inclusion criteria for reasons which included a higher DAS than allowed by inclusion criteria or too infrequent use of NSAID. A consort diagram illustrating recruitment is documented, Figure 3.1. All 30 patients who were recruited completed the 12-week intervention period.

Figure 3.1 – NSAID withdrawal study consort diagram



3.6.2 Study demographics

Of the 30 patients recruited to our cohort, 27% were male (n=8). The mean age of the patient cohort was 56.9 years (range 33-73 years), comparable to and typical of our clinic population. The median disease duration for the whole group was 11 years (range 1-40 years). The majority of recruited patients were towards the deprived end of the spectrum: median SIMD for the whole group 32.42 and 90% of the patients were in Carstairs group 3 or higher, as detailed in Table 3.1.

Table 3.1 – Deprivation scores of study participants

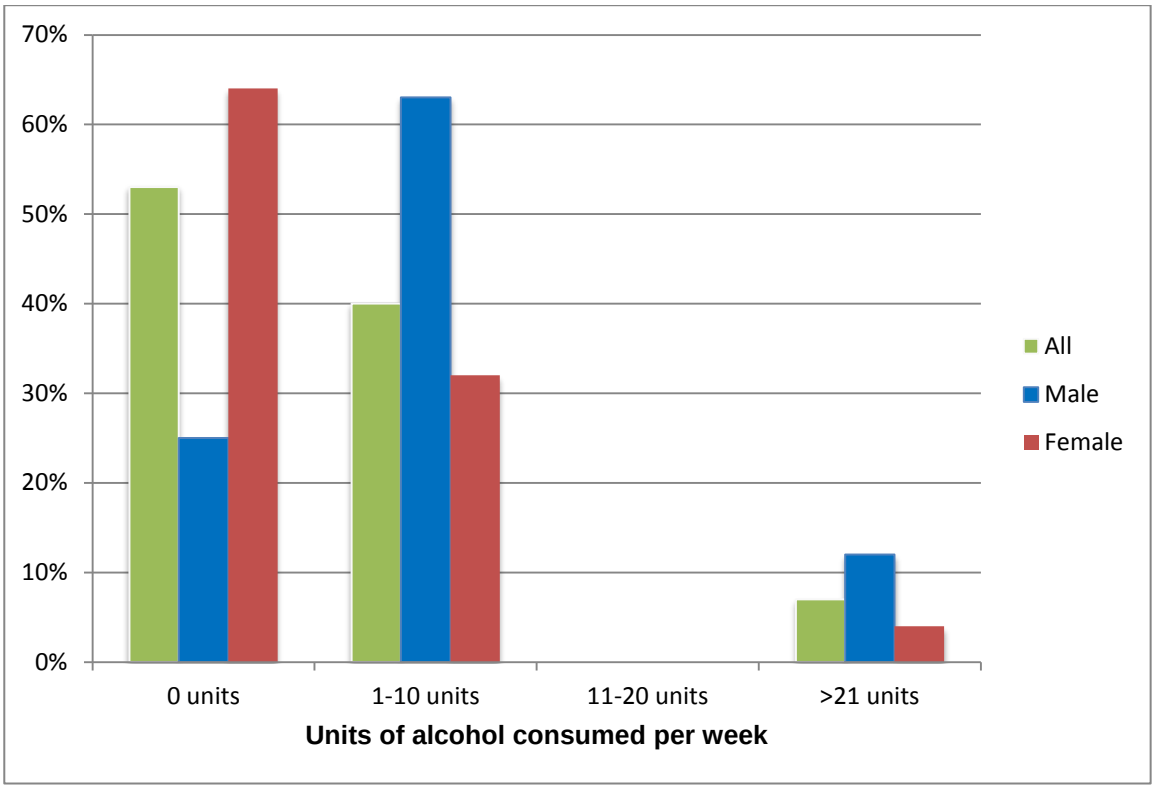
Deprivation Score	All (n=30)	Male (n=8)	Female (n=22)
Carstairs groupings			
1 & 2	10%	25%	4%
3, 4, 5	50%	37.5%	55%
6 & 7	40%	37.5%	41%
Median SIMD (and range)	32.42 (2.92-76.1)	33.995 (2.92-75.51)	32.415 (4.4-76.1)

Where Carstairs group 1 is the least deprived and Carstairs group 7 the most deprived

3.6.2.1 Alcohol consumption

A question about alcohol intake was included as a general study demographic as it was felt that there may be implications on GI symptoms depending on amount consumed. Alcohol intake was more than 20 units per week in only a small proportion of participants (<10%), Figure 3.2. The majority of female participants did not drink any alcohol.

Figure 3.2 – Alcohol consumption of study participants



3.6.3 Drug therapy at baseline

All patients were taking regular prescribed NSAID and this met study inclusion criteria; different preparations prescribed are documented in Table 3.2. Etodolac was the most frequently taken prescribed anti-inflammatory and this is discussed further in Section 3.7.2.1. The only 'true' COX2 inhibitor taken by patients recruited to the study was etoricoxib, taken by only 1 female.

Table 3.2 – Baseline anti-inflammatory therapy prior to study inclusion

	All (n=30)	Male (n=8)	Female (n=22)
Anti-inflammatory use	100%	100%	100%
Diclofenac	10% (n=3)	12.5% (n=1)	9% (n=2)
Etodolac	60% (n=18)	87.5% (n=7)	50% (n=11)
Etoricoxib	3% (n=1)	0	4% (n=1)
Meloxicam	10% (n=3)	0	14% (n=3)
Nabumetone	10% (n=3)	0	14% (n=3)
Naproxen	7% (n=2)	0	9% (n=2)

Only 1 patient was prescribed prednisolone before study recruitment, at a dose of 2.5mg per day. The dose of prednisolone was maintained at 2.5mg per day throughout study duration. Seven patients reported regular fish oil supplement consumption (5 males and 2 females).

Table 3.3 documents DMARD and biologic prescription of the study cohort. The median prescribed dose of methotrexate at study enrolment was 20mg per week; 21.25mg per week for males and 15mg per week for females. The median prescribed dose of sulfasalazine at study enrolment was 2.5g per day; 2.75g per day for males and 2g per day for females. Over 50% of study participants were prescribed combination DMARD therapy, again reflective of routine practice within the unit. All patients treated with gold received IM sodium aurothiomalate.

Of the 4 patients prescribed anti-TNF therapy, 3 were co-prescribed triple DMARD combination (methotrexate, sulfasalazine and hydroxychloroquine) and one co- prescribed methotrexate alone; all 4 of these patients were taking ≥20mg methotrexate per week. Of the anti-TNF drugs used, adalimumab was the commonest. None were prescribed etanercept and there were no other biologic therapies, such as rituximab, being used.

Table 3.3 – Disease modifying therapy prior to study inclusion

	All	Male	Female
Single DMARD	33.3% (n=10)	50% (n=4)	27% (n=6)
MTX	7% (n=2)	0	9% (n=2)
SSZ	23% (n=7)	37.5% (n=3)	18% (n=4)
LEF	3% (n=1)	12.5% (n=1)	0
Combination DMARD	53.3% (n=16)	25% (n=2)	64% (n=14)
MTX+SSZ	23% (n=7)	25% (n=2)	23% (n=5)
SSZ+HCQ	3% (n=1)	0	4.5% (n=1)
MTX+HCQ	10% (n=3)	0	14% (n=3)
MTX+HCQ+SSZ	10% (n=3)	0	14% (n=3)
MTX+gold	7% (n=2)	0	9% (n=2)
Anti-TNF	13.3% (n=4)	25% (n=2)	9% (n=2)
Adalimumab	10% (n=3)	25% (n=2)	4.5% (n=1)
Infliximab	3% (n=1)	0	4.5% (n=1)

HCQ = hydroxychloroquine, LEF = leflunomide, MTX = methotrexate, SSZ = sulfasalazine

3.6.4 Baseline cardiovascular demographics and risk factors

Table 3.4 documents the baseline CV information recorded at study commencement. Of the study participants, 20% were current smokers. Of the female participants, 18% were pre-menopausal and 82% post-menopausal. The median BMI for both males and females would be classified as "overweight" as it falls in the range 25-29.9 kg/m^2**.**

Median BP recording for the whole group was 141/87mmHg. According to the BHS classification guidelines (Table 1.6, (91)) this would be categorised as a Grade I (mild) hypertension for systolic BP reading and a high-normal diastolic BP reading. The range of both systolic and diastolic BP readings was from optimal to Grade III systolic and optimal to Grade II diastolic. Males had a higher median systolic BP than females, though females had a greater range of readings.

The median TC was elevated at >5mmol/l. Median HDL-cholesterol was surprisingly favourable at >1mmol/l, resulting in a TC: HDL ratio of <4 (except in males). Only 20% of the whole group were prescribed statins.

Table 3.4 – Cardiovascular demographics

	All (n=30)	Male (n=8)	Female (n=22)
Age	60	62	55
years	(33-73)	(53-73)	(33-70)
Current smoker	20% (n=6)	25% (n=2)	18% (n=4)
Systolic BP	141	143	139.5
mmHg	(109-190)	(128-156)	(109-190)
Diastolic BP	87	85	87
mmHg	(72-103)	(75-103)	(72-101)
Hypertension diagnosis	50% (n=15)	75% (n=6)	41% (n=9)
Total cholesterol	5.15	5.45	4.9
mmol/l	(3.4-7.4)	(3.4-6.2)	(3.4-7.4)
HDL cholesterol	1.4	1.2	1.5
mmol/l	(0.8-3.2)	(0.9-1.7)	(0.8-3.2)
TC:HDL ratio	3.4	4.25	3.2
	(1.0-5.6)	(2.5-6)	(1-5.1)
Triglycerides	1.05	1.5	1.0
mmol/l	(0.5-3.6)	(0.8-2.3)	(0.5-3.6)
Statin therapy	20% (n=6)	37.5% (n=3)	13.6% (n=3)
Weight	73.5	83	68
kg	(53-117)	(70-117)	(53-98)
BMI	26.57	27.40	26.56
kg/m^2	(22.04-44.74)	(22.84-33.1)	(22.04-44.74)

Medians (and ranges) shown

3.6.5 Primary outcome

3.6.5.1 Overall DAS44

There was no significant difference in DAS44 from baseline to 12 weeks, Table 3.5. A slight upwards trend was seen between baseline and 6 weeks in the overall group and in females. Comparing 6 and 12 week DAS44, a downwards trend was seen which was significant (p=0.033 whole group, p=0.012 females).

The median baseline DAS44 readings would classify the patients as having low disease activity (as previously described in Table 2.5). In the overall cohort at baseline, 7 were in remission (DAS44 <1.6), 16 had low disease activity (DAS44 1.6-2.4) and 7 moderate disease activity (DAS44 2.4-3.6); the inclusion criteria stipulated a DAS44 ≤2.8. By 12 weeks, 11 were in remission, 12 had low disease activity and 7 moderate disease activity.

There was no overall change in DAS44 components (ESR, swollen joint count, RAI or patient GH) over the 12 week intervention period and this will be discussed further in Sections 3.6.5.2-3.6.5.5.

Table 3.5 – DAS44 results

	Baseline	6 weeks	12 weeks	Wilcoxon signed-rank test
DAS44 All	2.08 (0.26-2.79)	2.19 (0.65-5.08)	1.79 (0.76-2.05)	0-6 weeks p=0.130 0-12 weeks p=0.781 6-12 weeks **p=0.033**
DAS44 Male	1.70 (0.26-2.79)	1.52 (0.65-3.25)	1.61 (0.76-2.78)	0-6 weeks p=0.674 0-12 weeks p=0.401 6-12 weeks p=0.779
DAS44 Female	2.13 (0.94-2.63)	2.35 (1.09-5.08)	1.88 (0.76-2.95)	0-6 weeks p=0.110 0-12 weeks p=0.405 6-12 weeks **p=0.012**

Medians (and ranges) shown

3.6.5.2 Components of DAS44 – ESR

ESR levels were low overall and remained so throughout the study; despite the anti-inflammatory intervention, Table 3.6. There was only a slight increase in ESR in the female participants between baseline and 6 weeks; this was only by 1.5mm/1st hour (p=0.039) and by 12 weeks had returned to baseline values.

Table 3.6 – ESR

	Baseline	6 weeks	12 weeks	Wilcoxon
ESR	5	8	7	0-6 weeks p=0.104
mm/1st hour	(2-35)	(2-51)	(2-38)	0-12 weeks p=0.152
All				6-12 weeks p=0.613
ESR	5	5	5	0-6 weeks p=0.684
mm/1st hour	(2-35)	(2-22)	(2-33)	0-12 weeks p=0.671
Male				6-12 weeks p=0.399
ESR	7	8.5	7	0-6 weeks p=**0.039**
mm/1st hour	(2-31)	(2-51)	(2-38)	0-12 weeks p=0.163
Female				6-12 weeks p=0.280

Medians (and ranges) shown

3.6.5.3 Components of DAS44 – Ritchie Articular Index

There was no significant difference in RAI by the 12-week point. Although the scores in the cohort overall increased marginally from baseline to 6 weeks, this was not statistically significant, Table 3.7. Females had an increase in this tender joint index from baseline to 6 weeks (p=0.039); however by 12 weeks this had returned to baseline levels (difference from 6-12 weeks, p=0.049).

Table 3.7 – Ritchie Articular Index

	Baseline	6 weeks	12 weeks	Wilcoxon
RAI All	2.5 (0-10)	4 (0-17)	2 (0-15)	0-6 weeks p=0.234 0-12 weeks p=0.422 6-12 weeks p=0.062
RAI Male	2 (0-10)	1 (0-15)	1 (0-15)	0-6 weeks p=0.730 0-12 weeks p=0.785 6-12 weeks p=1
RAI Female	3 (0-8)	4.5 (0-17)	2 (0-7)	0-6 weeks **p=0.039** 0-12 weeks p=0.403 6-12 weeks **p=0.049**

Medians (and ranges) shown

RAI = Ritchie articular index

3.6.5.4 Components of DAS44 – 44 swollen joint count

There was no significant difference in 44-swollen joint count by the 12-week point. There was a non-significant rise in median number of swollen joints from 4 to 5 between baseline and 6 weeks in the whole group, Table 3.8. Analysis of the female group confirmed that this was just significant (p=0.042). This was followed by a 2-joint decrease from 6 to 12 weeks (p=0.025) in the whole group.

Table 3.8 – Swollen joint count

	Baseline	6 weeks	12 weeks	Wilcoxon
Swollen joints All	4 (0-10)	5 (0-16)	3 (0-9)	0-6 weeks p=0.098 0-12 weeks p=0.489 6-12 weeks **p=0.025**
Swollen joints Male	2 (0-5)	2 (0-6)	3 (0-7)	0-6 weeks p=0.730 0-12 weeks p=0.863 6-12 weeks p=0.059
Swollen joints Female	4 (0-10)	5 (2-16)	4 (1-9)	0-6 weeks **p=0.042** 0-12 weeks p=0.362 6-12 weeks p=0.07

Medians (and ranges) shown

3.6.5.5 Components of DAS44 – Patient global health assessment

There was no significant difference in patient GH from baseline to the 12-week point and by then median GH assessment score had fallen to less than baseline levels in all 3 groups. Table 3.9 details a rise in patient GH assessment by a median of 14 points in the overall group by 6 weeks (p=0.009) and by 20 points in the female group (p=0.038). From 6 to 12 weeks there was a significant reduction in the whole and female groups, with patient GH scores falling by a median of 18 and 23 points respectively.

Table 3.9 – Patient global health assessment

	Baseline	6 weeks	12 weeks	Wilcoxon
PGHA	29	43	25	0-6 weeks **p=0.009**
VAS/100mm	(4-61)	(7-77)	(1-55)	0-12 weeks p=0.592
All				6-12 weeks **p=0.003**
PGHA	32	32	31	0-6 weeks p=0.093
VAS/100mm	(4-45)	(7-70)	(14-55)	0-12 weeks p=0.042
Male				6-12 weeks p=0.674
PGHA	27	47	24	0-6 weeks **p=0.038**
VAS/100mm	(4-61)	(11-77)	(1-55)	0-12 weeks p=0.733
Female				6-12 weeks **p=0.001**

PGHA = patient global health assessment. VAS = visual analogue score.
mm = millimetres

Medians (and ranges) shown

3.6.5.6 Components of DAS44 – pain score

There was no significant difference in pain score from baseline to 12 weeks. In the overall group, a significant increase in pain score was seen from baseline to 6 weeks, in addition to the separate analysis for females (p values <0.0001 and 0.001 respectively), Table 3.10. This reflects a median score rise of 17 points in the overall group and 20 points in the female group. However, the rise in male pain score was only by 1 point, yet was still significant (p=0.035). A subsequent significant fall in pain score was then seen from 6 to 12 week assessments (p=0.008). What remains uncertain is the impact of the therapeutic interventions given (discussed later in Sections 3.6.11 and 3.7) and whether they were implicated in the large rebound in figures.

Table 3.10 – Pain score

	Baseline	6 weeks	12 weeks	Wilcoxon
Pain score	20	37	25	0-6 weeks **p<0.001**
VAS/100mm	(4-53)	(7-72)	(1-72)	0-12 weeks p=0.118
All				6-12 weeks **p=0.008**
Pain score	32	33	34	0-6 weeks **p=0.035**
VAS/100mm	(4-51)	(7-66)	(6-70)	0-12 weeks p=0.123
Male				6-12 weeks p=0.574
Pain score	18	38	23	0-6 weeks **p=0.001**
VAS/100mm	(4-53)	(8-72)	(1-72)	0-12 weeks p=0.436
Female				6-12 weeks **p=0.002**

VAS = visual analogue score, mm = millimetres

Medians (and ranges) shown

3.6.6 Secondary outcome – blood pressure

A significant reduction in systolic BP was observed with anti-inflammatory withdrawal by 7mmHg from baseline to 12 weeks (p=0.037), Table 3.11. Maximum systolic BP recordings fell over time – at baseline, maximal reading was 190mmHg and by 6 and 12 weeks this was 170 and 171mmHg respectively. However, no significant change in diastolic BP was recorded, Table 3.12.

Twelve patients were on antihypertensive therapy at study commencement (3 mono-therapy and 9 combination therapy). Those on anti-hypertensives showed a greater reduction in systolic BP than those who were not prescribed this therapy but this change was, however, not significant (p=0.071).

Changes in systolic BP over the course of study participation for each individual participant are documented in Figure 3.3. Twelve patients demonstrated the largest drop in systolic BP from baseline to 6 weeks (numbers 2,3,6,9,13,15,17,18,19,21,24 and 25). Of these, 7 were on anti-hypertensive treatments (numbers 2,3,13,15,17,18 and 24).

Table 3.11 – Changes in systolic blood pressure

	Baseline	6 weeks	12 weeks	Wilcoxon
Systolic BP	141	136	133.5	0-6 weeks **p=0.025**
mmHg	(109-190)	(104-170)	(106-171)	0-12 weeks **p=0.037**
All (n=30)				6-12 weeks p=0.888
Systolic BP	143	133	134	0-6 weeks p=0.123
mmHg	(128-156)	(123-151)	(118-169)	0-12 weeks p=0.674
Male (n=8)				6-12 weeks p=0.674
Systolic BP	139.5	140	134	0-6 weeks p=0.107
mmHg	(109-190)	(104-170)	(106-171)	0-12 weeks **p=0.015**
Female (n=22)				6-12 weeks p=0.626

BP = blood pressure, mmHg = millimetres of mercury

Medians (and ranges) shown

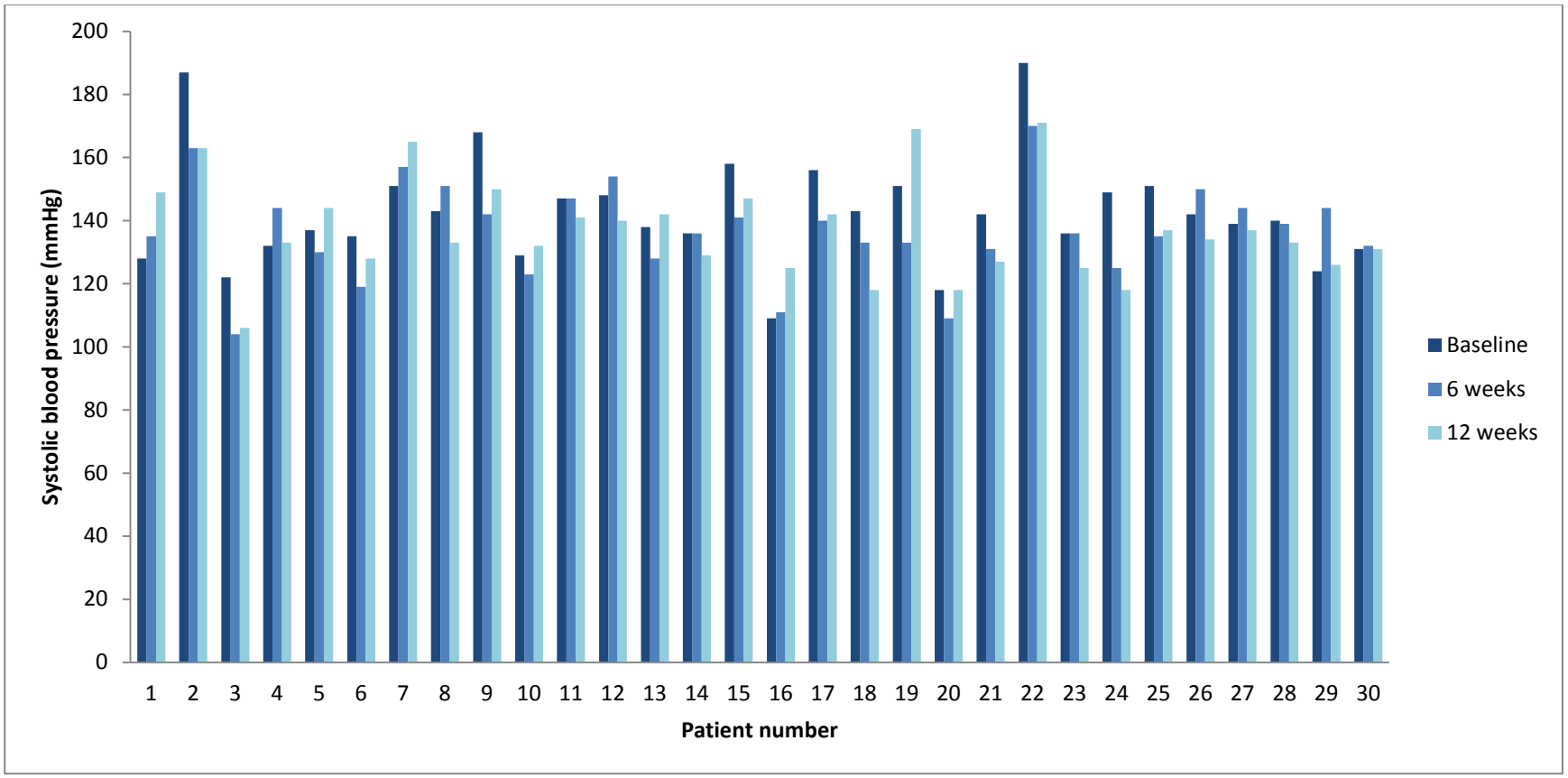
Table 3.12 – Changes in diastolic blood pressure

	Baseline	6 weeks	12 weeks	Wilcoxon
Diastolic BP	87	85	84	0-6 weeks **p=0.015**
mmHg	(72-103)	(66-99)	(72-105)	0-12 weeks p=0.245
All (n=30)				6-12 weeks p=0.319
Diastolic BP	85	86	85	0-6 weeks p=0.207
mmHg	(75-103)	(71-92)	(76-98)	0-12 weeks p=0.888
Male (n=8)				6-12 weeks p=0.723
Diastolic BP	87	84	83	0-6 weeks **p=0.027**
mmHg	(72-101)	(66-99)	(72-105)	0-12 weeks p=0.144
Female (n=22)				6-12 weeks p=0.414

BP = blood pressure, mmHg = millimetres of mercury

Medians (and ranges) shown

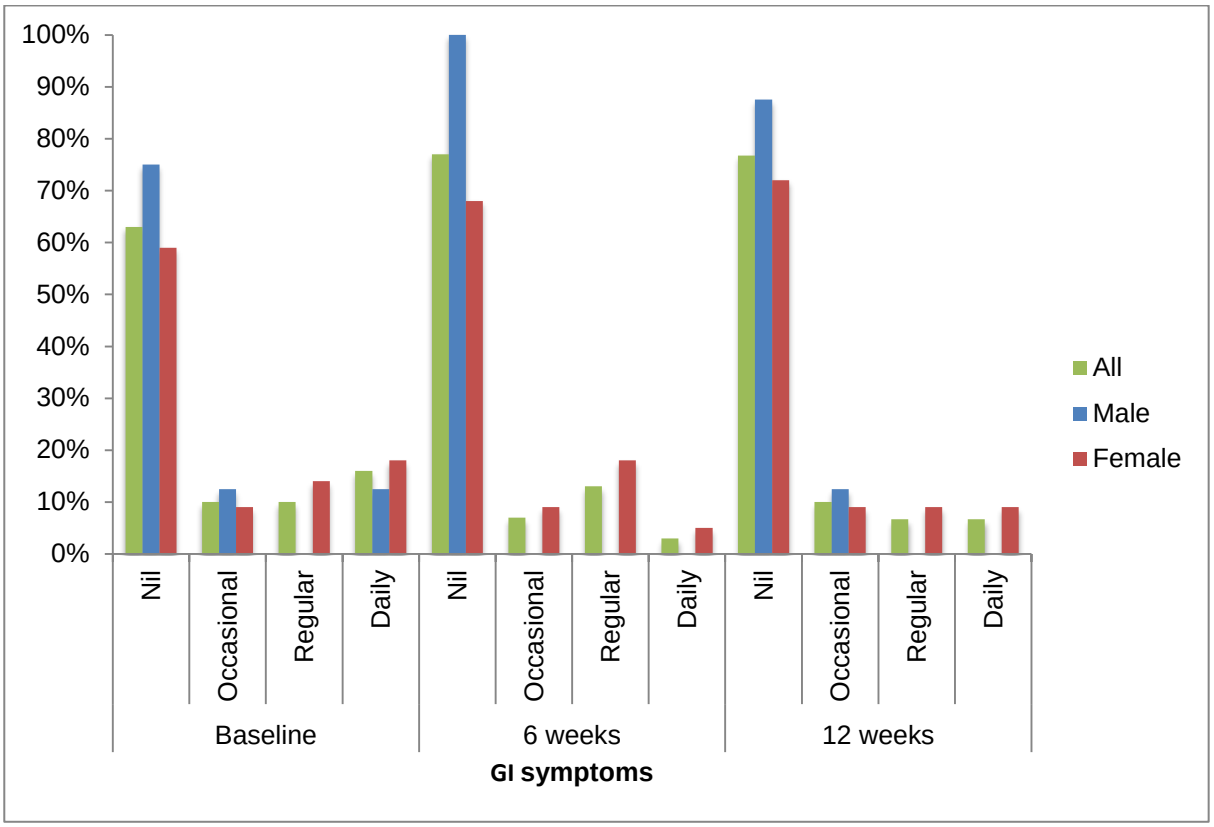
Figure 3.3 – Individual participants and changes in systolic blood pressure over course of study



3.6.7 Secondary outcome – gastrointestinal symptoms

At 63%, the majority of patients did not report any GI symptoms at baseline, Figure 3.4. This figure increased to 77% at 6 and 12 weeks. The number of patients reporting regular or daily upper GI symptoms (e.g. reflux, heartburn or indigestion) fell from 27% at baseline to 16% at 6 weeks and 14% at 12 weeks.

Figure 3.4 – Gastrointestinal symptoms



3.6.8 Secondary outcome – renal function

Males had a higher median baseline urea (7.8 mmol/l) compared with females (5.45 mmol/l), data not shown. A significant reduction in urea was seen within the whole group from baseline (5.95 mmol/l) to 12 weeks (4.8 mmol/l), p=0.018. No significant change in eGFR was shown (Table 3.13).

Table 3.13 – Changes in eGFR

	Baseline	6 weeks	12 weeks	Wilcoxon
eGFR ml/min/1.73m^2 **All**	71.5 (35-94)	73.5 (41-111)	72.5 (36-93)	0-6 weeks p=0.246 0-12 weeks p=0.284 6-12 weeks p=0.801
eGFR ml/min/1.73m^2 **Male**	72 (65-83)	75.5 (68-81)	72.5 (71-87)	0-6 weeks p=0.438 0-12 weeks p=0.041 6-12 weeks p=0.595
eGFR ml/min/1.73m^2 **Female**	71.5 (35-94)	73 (41-111)	70 (36-93)	0-6 weeks p=0.475 0-12 weeks p=0.751 6-12 weeks p=0.972

Medians (and ranges) shown

eGFR as calculated by the abbreviated MDRD equation (403)

3.6.9 Secondary outcome – functional assessment

The results detailed in Table 3.14 show that at baseline, the median physical component summary score below 50 and therefore below average physical function. The median mental component summary scores were all above average as shown in Table 3.15. There was no significant change in physical or mental scores from baseline to 12 weeks. There was a non-significant trend towards a reduction in physical component score from 0 to 6 weeks. By 12

weeks there was a significant improvement in this parameter in all groups to a median score higher than baseline and closer towards an average physical function score expected for the general population.

Table 3.14 – SF-12: physical component

	Baseline	6 weeks	12 weeks	Wilcoxon
PCS All	37.4 (24.5-56.6)	34.3 (24.5-55.1)	40.25 (31.6-56.7)	0-6 weeks p=0.449 0-12 weeks p=0.30 6-12 weeks **p=0.001**
PCS Male	37.35 (25.2-46.6)	32.7 (28-44.7)	38.75 (33.8-43.1)	0-6 weeks p=0.401 0-12 weeks p=0.208 6-12 weeks **p=0.017**
PCS Female	37.4 (24.5-56.6)	37.2 (24.5-55.1)	40.45 (31.6-56.7)	0-6 weeks p=0.677 0-12 weeks p=0.072 6-12 weeks **p=0.012**

PCS = physical component summary Medians (and ranges) shown

Table 3.15 – SF-12: mental component

	Baseline	6 weeks	12 weeks	Wilcoxon
MCS All	54.35 (30.4-66.5)	54 (27.1-63.4)	54.5 (38.4-66.1)	0-6 weeks p=0.682 0-12 weeks p=0.478 6-12 weeks p=0.673
MCS Male	55.7 (30.4-60.4)	58.1 (38.1-61.3)	50.3 (38.4-62.2)	0-6 weeks **p=0.028** 0-12 weeks p=0.779 6-12 weeks p=0.161
MCS Female	54.05 (37.9-66.5)	52.8 (27.1-63.4)	54.75 (40.1-66.1)	0-6 weeks p=0.543 0-12 weeks p=0.638 6-12 weeks p=0.192

MCS = mental component summary Medians (and ranges) shown

3.6.10 Safety and tolerability

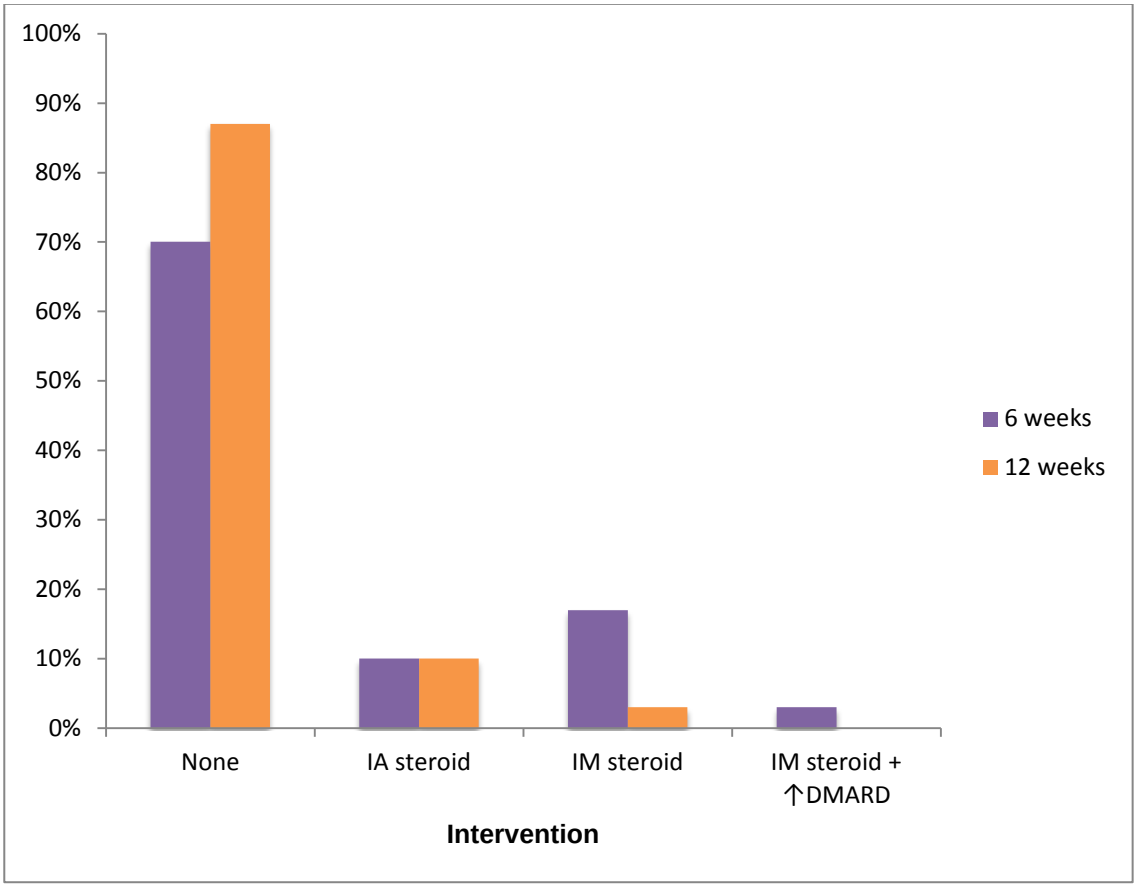
All 30 patients completed the study without requiring re-introduction of NSAID. No adverse effects from routine DMARD or anti-TNF therapy were documented.

3.6.11 Interventions required and corticosteroid administration

All patients kept a diary in which they recorded on how many days they needed to take non-NSAID analgesia. In the 42 days between visits 1 and 2, and visits 2 and 3, the patients took analgesia on a mean of 12 and 10 days (respectively).

The number of steroid injections administered and any changes in DMARD were also recorded and are displayed in Figure 3.5. Seven IM and 6 IA steroid injections were administered to 11 patients from a total of 60 follow-up visits. At the 6 week visit, 6 IM and 3 IA steroid injections were given. At the 12 week visit, 1 IM and 3 IA steroid injections were given. Conversely, at the 6 and 12 week visits, 70% and 87% respectively did not require any intervention.

Figure 3.5 – Interventions required



3.7 DISCUSSION

3.7.1 Demographics

3.7.1.1 General

27% of the recruited cohort were male, a higher proportion than is often seen in RA investigatory cohorts. In previously published general RA studies, the male participation rates have usually been lower than female; the MASCOT study had a male population of 22% of total (408). The significance of this difference is uncertain and could be interpreted as a patient's interest to participate in a study where less rather than more medication is taken.

The high median SIMD and Carstairs groupings reflected the population demographics of the recruiting hospital. The low alcohol intake statistics are likely in part to reflect advice given about minimising alcohol consumption when taking DMARD therapy, especially methotrexate.

3.7.1.2 Cardiovascular

47% were ever smokers (data not shown) and 20% current smokers – this mirrors average Scottish national figures as previously discussed in Section 1.4 (64). The post-menopausal status of over 80% of the female participants reflected the median age of 55 years. The hormonal changes after a female passes through the menopause, namely oestrogen withdrawal, is a documented risk factor for CVD – oestrogen reduction is said to have a unfavourable effect on CV function and associated metabolism (409). The prescription of statins in only 20% of the cohort is perhaps a surprisingly low figure given the recent emphasis on monitoring and addressing this CV risk factor in the primary care setting; however the lower median age of the female participants may partly explain this lower figure.

3.7.2 Drug therapy

3.7.2.1 Anti-inflammatories

60% of the total group were prescribed etodolac as their anti-inflammatory. This is reflective of the prescribing practice of the Centre for Rheumatic Diseases at Glasgow Royal Infirmary at the time of study recruitment. Etodolac is an interesting anti-inflammatory as while it is classed as a traditional non-steroidal anti-inflammatory; it does have significant COX2 inhibition properties including less GI side-effects than other non-selective NSAID (410) (411) (412) (413) (414).

3.7.2.2 DMARD

Methotrexate use was at the level of 70% in this cohort, either as mono-therapy or in combination with another DMARD and / or anti-TNF. The median dose for the whole group was 20mg per week (as discussed in section 3.x) with the range being 12.5-25mg per week in males and 5-27.5mg per week. The higher upper limit of the ranges does reflect the use of this DMARD at the time of study recruitment, where doses in excess of 25mg per week were occasionally used within the department: of note is that as per Section 3.3.3 (Step 3) we did not escalate beyond 25mg per week if there was loss of disease control, however, the patient prescribed 27.5mg per week was already established on this dose and it was not increased further during the study. Additionally, the 2.5mg per

week per month dose escalation of methotrexate would now be considered unnecessarily slow, but again reflects policy of the unit at that time.

Sulfasalzine was also prescribed in 70% of the cohort as mono-therapy or in combination with another DMARD and / or anti-TNF at the time of recruitment. Currently within the unit, methotrexate would be used preferentially to sulfasalazine, especially as mono-therapy.

3.7.3 Primary outcome

There was no significant difference in DAS44 from baseline (median 2.08) to 12 weeks (median 1.79). The individual DAS44 components (ESR, RAI, 44-swollen joint count and patient GH score) did not change between these 2 time-points. When the 6-week results are looked at, there was often a rise seen at this point only which then fell back to baseline values by 12 weeks.

The low overall ESR levels were to be expected in a group with a well-controlled inflammatory component of their disease. While the female cohort showed a significant increase in median patient GH from baseline to 6 weeks, interestingly, the male group showed no change. This may be due to a higher median baseline DAS44 score in the females, reflecting a higher level of disease activity in our female compared to our male cohort (2.13 versus 1.70). It is possible that at the mid-way visit at 6 weeks, our discussions regarding use of analgesia and review of the individual's progress went some way to reassure them and altered the patient reported scores of GH and pain.

3.7.4 Secondary outcomes

3.7.4.1 Blood pressure

There was a 5mmHg reduction in systolic BP ($p=0.037$) from baseline to 6 weeks and a 7mmHg reduction in systolic BP from baseline to 12 weeks ($p=0.025$); no change in diastolic BP was seen. It is not certain whether anti-inflammatory drug withdrawal alone contributed to this impressive reduction. A contributing factor may have been patients becoming accustomed to the study environment in the 6 and 12 week visits, feeling more relaxed and subsequently lower BP recordings documented. An increase in median pain score at 6 weeks was discussed in Section 3.6.5.6; one may have expected this clinical feature to be associated with a higher BP reading in the absence of any other intervention.

3.7.4.2 Gastrointestinal symptoms

By 12 weeks, the percentage of patients reporting GI symptoms had reduced from 37% to 23%. The lesser reporting of clinically noticeable GI irritation, after withdrawal of anti-inflammatory medication mirrors clinical studies, as previously discussed in Section 1.7.7.

3.7.4.3 Renal function

The relationship between anti-inflammatory use and renal function has been outlined previously in Section 1.7.6. The data presented here varies slightly from previously published work where the effect of NSAID withdrawal on renal function was studied: Unsworth et al had documented a significant reduction in creatinine and a trend of urea reduction, although not significant (272). The lack of association between urea and creatinine / eGFR reduction in this study may be explained in part by the differing preparations of anti-inflammatory previously taken, co-prescription of medication (e.g. antihypertensives, other cardiac medications), state of hydration or indeed differing muscle mass or degree of muscle atrophy in each participant (273). We did not document the trend in renal function prior to study involvement.

3.7.4.4 Functional assessment

The below average physical function scores could easily be attributed to the effect RA has on the participants' daily function due to joint disease. The median disease duration of study participants was 11 years (as described in Section 3.6.2) and it is likely that patients had a degree of secondary mechanical as well as inflammatory pathology affecting their joints, in turn contributing to a higher physical component score.

3.7.5 Interventions

Unfortunately, no pre-study analgesia diary was available with which to make a comparison. While we asked the patients to document use of analgesia for musculoskeletal pain, we cannot exclude use for dysmenorrhoea, dental pain etc.

It seems unlikely that the small amount of steroids given at the 6 and 12 week time-points would have been sufficient to have caused the overall dramatic reduction in patient GH Assessment scores.

We did see patients for symptoms that would not necessarily be attributed to increased activity of their RA, e.g. headache and neck pain. The patient who reported increased headache after anti-inflammatory withdrawal was examined further, appropriate investigations ordered and a neurology opinion sought (no significant intra-cranial abnormality was found on computed tomography scan of head).

3.8 LIMITATIONS OF THE STUDY

The study was open labelled, non-randomised and included only 30 subjects. Twelve weeks is possibly too short an interval to assess whether a more extended NSAID withdrawal can be achieved and maintained in the long term. NSAID was discontinued at study enrolment (the baseline visit) – NSAID differ in their half-lives and by the 6-week visit it is possible that some patients will have had a slower initial effect of NSAID withdrawal than others due to different preparations prescribed (221) (296). Any difference in this regard would have been eliminated by the time of 12-week review.

There was no control arm in the study. In order for a fair assessment if we were to have carried out a study comparing patients continuing NSAID versus those whose therapy was discontinued, each 'study patient' would have needed to be matched with a 'control' taking the exact same preparation and dose of NSAID. This would have been a logistical problem. Additionally, the preparation and dose of DMARD or steroid would have needed to be identical also. Perhaps an alternative approach may have been to use the patients as their 'own control', comparing observations from before anti-inflammatory withdrawal with those after.

One other proposed methodology discussed was to randomise patients to either continuation of NSAID or switch to placebo to induce NSAID withdrawal. This would have involved converting all study participants to the same NSAID prior to introducing placebo to half of them, or obtaining multiple matching placebos to

account for all of the different NSAID preparations and doses the patients were taking. Unfortunately due to the time, practical and financial constraints of this study we were unable to adopt any of these suggestions.

Only patients with moderately active (or less) RA were enrolled. The LREC were opposed to our initial intention of withdrawing NSAID from patients with more active RA; we therefore specified in our inclusion criteria a DAS44 of ≤2.8 to gain approval to commence the study (see section 3.2.1). As well as recording DAS44 and pain scores, the additional documentation of EMS may have been informative as a patient-reported variable of inflammatory disease activity.

The relationship between withdrawal of NSAID and reduction in systolic BP remains hypothetical. A randomised controlled trial would be helpful to clarify this further, but there would be inevitable difficulties of conducting such a study, as highlighted above. There is a possibility that the reduction in systolic BP may have been a routine observation over time and perhaps a more prolonged charting of BP pre- and post-withdrawal may have been helpful. There is a possibility that the participants may have become accustomed to the study environment during the course of their visits, with resultant relaxation and drop in BP. The study is too small to reliably investigate whether the BP changes were confined to particular levels or ranges.

We did not have a pre-study review of whether the 13 steroid injections, administered at the 6-week visit, were different from the patients' usual requirements. Even a medical case-note review of a set time period before study enrolment may not be accurate, as GPs may have given steroid injections in the community without our knowledge.

With regards to change in renal function we did not document the individual's state of hydration nor make any review with regards to the stability of urea or creatinine prior to enrolment in study.

In broader terms, we have not been able to confirm if these patients are a true representation of a typical RA cohort – all were RF positive, but information on previous DMARD and presence of erosions is not available.

3.9 BENEFITS IDENTIFIED

These are discussed further in Section 6.1.2. It is reasonable to expect that these results could allow the design of a larger and more comprehensive study to inform the management and treatment of patients with RA. This study was designed as a feasibility study intended to inform future work.

The early increase in pain scores after discontinuing NSAID suggests that a tapered withdrawal might be associated with less of an increase in discomfort. Overall the intervention was well accepted by patients once enrolled; there were no drop-outs and all completed the 12-week intervention period without recommencing NSAID. Additionally, there was a maintained trend in reduction of reported upper GI symptoms. BP was the only CV risk factor which changed with this intervention.

Despite the above limitations this is the first supportive evidence to implement guidance of limiting NSAID use in patients with low DAS score without adversely affecting their quality of life or disease control. Additionally, there was no need for significant additional input. We have demonstrated additional benefits on systolic BP control that has important implications for reducing CV risk. Future studies of CV risk in RA should take into account the influence of NSAID-induced hypertension.

3.10 SUMMARY

This study confirms that anti-inflammatory withdrawal was acceptable to and achievable by patients, alongside support from medical staff, at up to 12 weeks of follow-up. The rationale that NSAID withdrawal plus intervention would provide equivalent symptom control to that achieved by continuing therapy has been borne out by the reassuring minimal changes in DAS44 (and individual components) and relatively few interventions required from baseline through to 12 weeks. There was an impressive reduction in systolic BP seen with this intervention which raises many interesting issues for future management of patients with inflammatory arthritis with regards to the advancing area of CV risk management. A reassuring profile of improvement in GI symptoms was also noted. The results of this study pose a further question, which is not able to be

answered within the confines of this research, which is, do patients with a low DAS require NSAID therapy at all?

3.11 ACKNOWLEDGMENTS

Sisters Rosemary Hampson assisted with patient recruitment and study co-ordination as well as providing additional metrology. Ms Ann Tierney was crucial for study administration, database management and statistical assistance. I would like to acknowledge registrars and consultants from the Centre of Rheumatic Diseases at Glasgow Royal Infirmary for their assistance in identifying suitable patients from their clinics for this research study.

CHAPTER 4

A Pilot Study of a Mediterranean-Type Diet Intervention in Female Patients with Rheumatoid Arthritis

4.1 INTRODUCTION

A Mediterranean-type diet has been shown to have many potential health benefits. These include reduction in CV risk (318) (319) (330) and improvement in RA disease activity (346) as previously outlined in Section 1.8. It is not clear, however, whether such a diet could achieve beneficial results in patients with RA in a true to life setting, particularly in a population with high levels of social deprivation such as Glasgow. It is well established that any intervention requiring a change in lifestyle or behaviour, especially those which may be life-long and culturally driven, is difficult to achieve and sustain.

4.2 JUSTIFICATION OF STUDY DESIGN AND PROTOCOL

The primary outcome of the pilot study was to assess the influence of a Mediterranean-type diet intervention on clinical and laboratory parameters of RA disease activity and the CV system at 6 months. The secondary outcomes were to assess the influence of this diet on food intake frequencies at 3 months and the overall practicality to participating patients by obtaining specific feedback. Existing resources were targeted to be used as much as possible.

One hundred and thirty female patients with RA aged between 30 and 70 years old were recruited over a 9 month period. Females were chosen rather than males as it was felt that recruitment to a dietary lifestyle study would have been quicker due to the demographics of patients served by the hospitals.

Three hospital sites in Glasgow were used: Royal Infirmary, Southern General and Stobhill Hospital. These sites were chosen with the aim of recruiting patients from within one of the Social Inclusion Partnership areas in Glasgow, areas of social deprivation (384) (385).

The study was approved by the LREC and patients gave written informed consent.

4.2.1 Inclusion criteria

Female patients aged between 30 and 70 years old with a diagnosis of RA made by a Consultant Rheumatologist were considered for inclusion. All were under the care of 1 of the 3 hospital rheumatology departments noted above and were

able to give written informed consent. There were no specific stipulations regarding RA therapy. To recap Section 2.3.2, suitable patients were either identified during the clinic consultation or from within multi-disciplinary team discussions. If thought appropriate they were invited to take part in the study and were provided with a Patient Information Sheet (Appendix V). Potential recruits were telephoned at home to invite them to a baseline assessment if they wished to proceed with study involvement. All recruited patients gave written informed consent (Appendix VI).

4.2.2 Exclusion criteria

Males, pregnant women or women contemplating pregnancy were excluded from this study. Inability to give written informed consent resulted in exclusion from participation in the study also.

4.2.3 Allocation to intervention or control groups

We aimed to recruit 180 participants but were limited to 130 within the constraints of the study time period. The intention had been for random allocation of patients to intervention and control groups. However, a major limiting factor of the study was the availability of the weekly cookery courses in a location close to the patient's home and at a time suitable to them. Consequently a more pragmatic approach was necessary. This resulted in those able to attend on certain course dates being allocated to the intervention group and those unavailable on dates of programmed courses, for whatever reason, becoming the control group. Transport was provided in a small number of cases to allow easier access to classes.

The 75 patients allocated to the intervention group attended 2 hour sessions on a weekly basis over a 6-week period. There was a maximum of 10 participants in each group to encourage interaction and promote a relaxed environment. The sessions were called "Get Shopping, Get Cooking" and were delivered by nutritionists and teaching staff from NHS Greater Glasgow's Health Promotion Department. Occupational Therapy staff advised on the provision of aids for food preparation, primarily to help patients with impairment of hand function due to their arthritis. The course content included food hygiene, food storage and nutrition labelling. Advice was also given regarding shopping and local access to affordable ingredients. During the programme, activities such as blind

tasting and practical cooking sessions allowed a variety of different foods to be rated for appearance, taste and texture. Each week the participants in the cooking classes prepared and cooked a meal which they were then able to take home and share with family or friends. This hands-on cooking and discussion was backed-up with written information (Appendix IX and X). Each folder contained information on a Mediterranean-type diet, healthy eating and recipes which promoted the increased consumption of fruits, vegetables and legume, along with the substitution of saturated fat with monounsaturated fat in the form of olive oil or spreads containing olive oil. The cost per patient for the 6 week course was £84 and this was met by the Greater Glasgow Health Board's Health Board Promotion Department.

The 55 patients in the control group received readily available written information on healthy eating only and did not attend the cookery course (Appendix IX and X).

4.3 SAFETY AND MEDICATION DOCUMENTATION

Any adverse event, including the onset of a new illness and the exacerbation of pre-existing conditions were to be reported and documented in study notes and in medical case records: nature of event, start and stop dates, severity, relationship to intervention and outcome. Any serious adverse event such as death, life-threatening adverse event or significant disability or incapacity was to be notified to the Chief Investigator within 24 hours. This would then be discussed with the local Ethics team. Planned surgery or hospitalisation, agreed upon before inclusion in the study, was not classified as a serious adverse event.

Any increase in DMARD dose or change in therapy was allowed to be undertaken by any Rheumatologist routinely reviewing the patient in clinic. Local recommendations for increasing doses and monitoring of DMARD therapy were adhered to. If significantly abnormal laboratory values occurred (which are seen on occasion with standard DMARD dose escalation) they were documented and acted upon as felt appropriate. Possible subsequent interventions included DMARD dose reduction, DMARD being withheld for a period of time and withdrawal of therapy altogether.

4.4 STUDY ASSESSMENTS

Patients in both groups were assessed on four occasions: screening, baseline (=0), 3 and 6 months. At the screening visit, the study was explained to the patient. Printed information previously provided was reviewed and written informed consent obtained. Food diaries were issued and their completion discussed. Patients were allocated to intervention or control groups as detailed above.

4.4.1 Demographics

Baseline demographic information was collated: age, disease duration, height and weight (and hence BMI), smoking status, alcohol consumption and Carstairs scores (for the purposes of analysis, groups 1 & 2, 3 4 & 5 and 6 & 7 were combined) (376).

4.4.2 Clinical and laboratory assessments

Clinical features were documented at 0, 3 and 6 months: 28 swollen and tender joint count, patient GH score (VAS/100mm), calculated DAS28, patient global pain score (VAS/100mm), duration of early morning stiffness (minutes), HAQ and BP. At the same time points the following laboratory variables were documented: ESR, CRP, TC, HDL cholesterol and TC: HDL ratio.

4.4.3 Dietary assessments

Dietary assessments included: FFQ, additional questions regarding fruit consumption, the intake of selected nutrients and food groups (to specifically assess Vitamin A, C and E intake, through food diaries) and documentation of the number of servings per week of fruit, vegetables and legumes, as well as combined amounts (FVL).

4.5 STATISTICAL METHODS

SPSS version 15.0 software was used for statistical analysis. Non-parametric statistical tests were used. Wilcoxon signed-rank test was used for within-group comparison at different time points. Mann-Whitney U test was used for comparison between intervention and control groups. Statistical significance was set as a p-value of <0.05 (see also Section 2.9 for additional statistical information).

4.6 RESULTS

4.6.1 Study demographics

Disease duration and BMI were similar in both intervention and control groups, Table 4.1. The median age of the control group was 53 years, which compared with 58 years in the intervention group. This was, however, not significant (p=0.131).

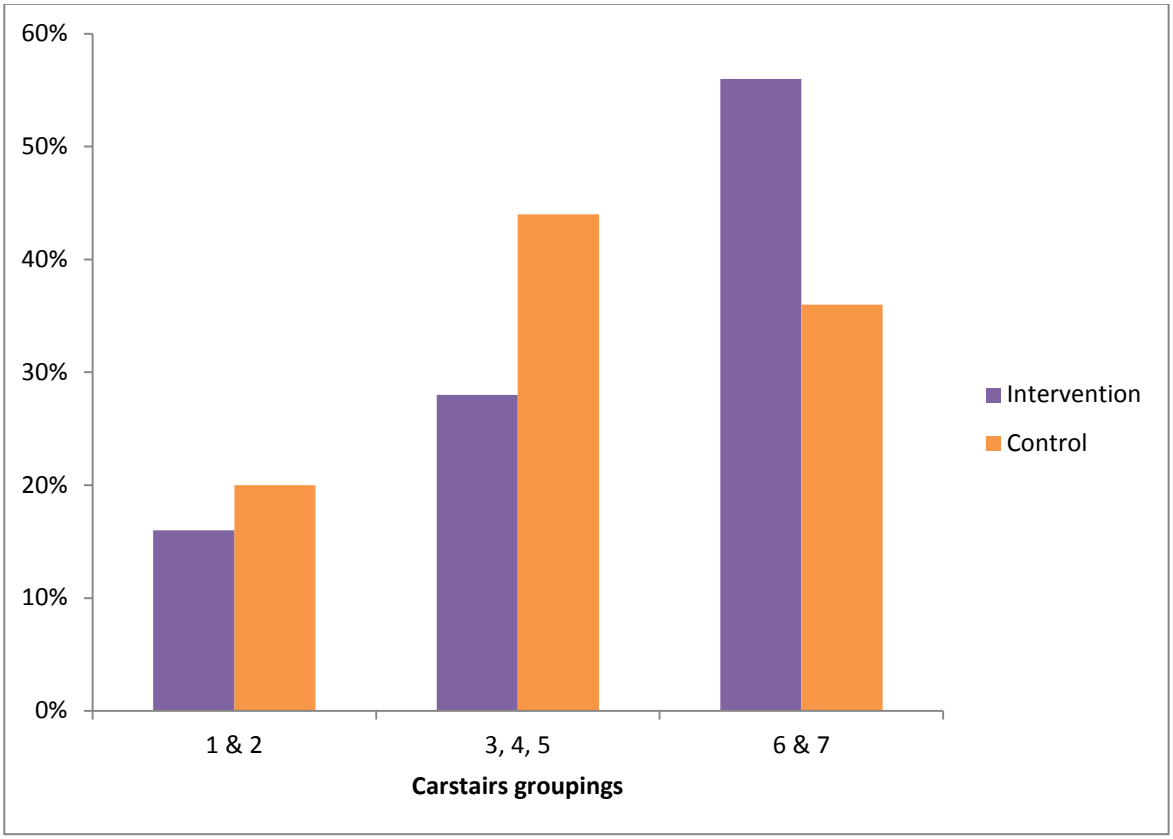
By designing this study to include individuals from Social Inclusion Partnership areas, it was foreseeable that a high proportion of participants would come from the most deprived social groups: 56% of the intervention group were in Carstairs group 6 or 7. Only 16% of the intervention group and 20% of the control group were in Carstairs group 1 and 2. These results are illustrated in Figure 4.1.

Table 4.1 – Baseline demographics for intervention and control groups

	Intervention (n=75)			**Control** (n=55)		
	Median	**Mean**	**Range**	**Median**	**Mean**	**Range**
Age years	58	55	30-70	52	53	30-71
Disease duration years	7	9.3	0.8-30	7	9.6	1-39
Height metres	1.61	1.60	1.45-1.75	1.62	1.61	1.48-1.73
Weight kg	66	66.4	65.1	70	70	72.5
BMI kg/m^2	25.86	26.75	18-47	27.65	27.95	17-45

kg = kilograms, m= metres

Figure 4.1 – Deprivation categories of enrolled patients



4.6.2 Drug therapy

DMARD treatment over the duration of the study was reviewed, with escalation or additional treatment being noted. Within the 6 month study period, 21% of the intervention group and 24% of the control group had such a change in their treatment. At baseline, 48% of the intervention group and 46% of the control group were prescribed methotrexate. By the time of study completion, these figures were 44% and 51% respectively, no statistically significant difference between the time points. A lower percentage of patients were taking methotrexate in the Mediterranean-type diet study than in the NSAID withdrawal study – this likely reflects the prescribing patterns of the earlier recruitment time of the dietary intervention study.

4.6.3 Primary outcomes

4.6.3.1 Clinical parameters

Intervention and control groups were relatively well matched at baseline (despite the previously described enforced pragmatic approach to randomisation) with regards to HAQ, pain score, tender and swollen joint counts and calculated DAS28.

Clinical assessments are shown in Table 4.2 and demonstrate a significant benefit in certain parameters in the intervention group compared with control group (Mann-Whitney calculations). At 6 months there was an improvement in patient GH assessment by 5 points in the intervention group, which compares with a deterioration of 9 points in the control group (p=0.002). There was no significant difference in DAS28 overall, or components of swollen or tender joint count.

Between group analyses confirmed a significant improvement in pain score between intervention and control groups at 3 and 6 months (p=0.011 and 0.049 respectively), in HAQ at 3 months (p=0.03) and in EMS at 6 months (p=0.041), Table 4.3. Wilcoxon signed ranks test analysis of the intervention arm demonstrated a significant reduction in EMS between 0 and 6 months (p=0.013).

4.6.3.2 Laboratory parameters

The control group at baseline demonstrated a much narrower range of ESR and CRP readings, which was not seen at other time points, Table 4.4. Although there was a numerical reduction in median ESR in each group by 6 months, this was not significant (p=0.234 intervention, p=0.485 control by Wilcoxon signed ranks test). There was no statistically significant difference in either ESR or CRP when intervention and control groups were compared. Therefore no direct conclusions on the benefit of a Mediterranean-type diet on haematological parameters in the form of inflammatory markers can be drawn

Table 4.2 - Clinical parameters: DAS28

	Intervention (n=75)			Control (n-55)			Mann Whitney
	Baseline	**3 months**	**6 months**	**Baseline**	**3 months**	**6 months**	(between groups)
DAS28	4.7 (1.5-7.13)	4.5 (1.75-8.01)	4.4 (1.04-7.14)	5.0 (1.12-6.9)	4.7 (0.49-7.13)	4.8 (0.14-7.04)	3 months p=0.439 6 months p=0.143
Tender joint count 0-28	5 (0-28)	5 (0-26)	4 (0-26)	6 (0-28)	6 (0-21)	6 (0-28)	3 months p=0.823 6 months p=0.088
Swollen joint count 0-28	6 (0-16)	5 (0-15)	4 (0-14)	6 (0-17)	5 (0-12)	5 (0-18)	3 months p=0.629 6 months p=0.676
Patient GH VAS 0-100mm	50 (0-100)	50 (0-100)	45 (0-95)	54 (10-95)	55 (0-100)	63 (10-85)	3 months p=0.60 6 months p=0.002

GH= global health, VAS = visual analogue score, mm = millimetre Median (and ranges) shown

Table 4.3 – Other clinical parameters of disease activity and function

	Intervention (n=75)			Control (n-55)			Mann Whitney
	Baseline	**3 months**	**6 months**	**Baseline**	**3 months**	**6 months**	(between groups)
Pain score VAS 0-100mm	50 (0-100)	50 (0-100)	50 (0-100)	55 (16-87)	62 (0-100)	63 (0-100)	3 months p=0.011 6 months p=0.049
Early morning stiffness mins	30 (0-720)	30 (0-720)	15 (0-720)	60 (0-720)	30 (0-720)	30 (0-720)	3 months p=0.156 6 months p=0.045
HAQ	1.75 (0.2-2.875)	1.625 (0.125-2.875)	1.625 (0-3)	1.75 (0.2-2.875)	1.875 (0-2.875)	1.875 (0-3)	3 months p=0.032 6 months p=0.79

mm = millimetre, mins= minutes

Medians (and ranges) shown

Table 4.4 – Inflammatory markers

	Intervention (n=75)			Control (n-55)			Mann Whitney
	Baseline	**3 months**	**6 months**	**Baseline**	**3 months**	**6 months**	(between groups)
ESR mm/1st hour	19 (2-101)	20 (1-105)	19 (1-54)	55 (16-87)	19 (2-65)	16 (1-92)	3 months p=0.738 6 months p=0.312
CRP mg/l	30 (0-720)	30 (0-720)	15 (0-720)	60 (0-720)	30 (0-720)	30 (0-720)	3 months p=0.485 6 months p=0.530

mm = millimetres, mg= milligrams, l=litre

Medians (and ranges) shown

4.6.3.3 Cardiovascular parameters

64% of the intervention group and 62% of the control were ever smokers.

There was no significant difference in median or range of BP readings between the intervention and control groups at the 3 assessment time points. Within group analysis was performed to see if there was evidence of a more subtle change in BP over time within the intervention group. Wilcoxon signed-rank analysis revealed a significant reduction in systolic BP by 4mmHg at 6 months in the intervention group (p=0.016), while the control group showed no such difference (p=0.968). This is as documented in Table 4.5 below.

Table 4.5 – Within group analysis of systolic BP changes

Systolic BP	Baseline	3 months	6 months	Wilcoxon
Intervention mmHg	132 (96-193)	130 (98-190)	128 (100-195)	**p=0.016**
Control mmHg	130 (99-191)	129 (87-190)	130 (97-130)	p=0.968

mmHg= millimetres of mercury

Medians (and ranges) shown

Table 4.6 documents clinical CV parameters recorded during study visits. The within group analysis of BP has already been discussed above. Using Mann-Whitney analysis, there were no significant differences in cholesterol or BP readings between groups. There was a non-significant reduction in weight in the intervention group.

Table 4.6 - Clinical cardiovascular parameters

	Intervention (n=75)			Control (n-55)			Mann Whitney (between groups)
	Baseline	**3 months**	**6 months**	**Baseline**	**3 months**	**6 months**	
Systolic BP mmHg	132 (96-193)	130 (98-190)	128 (100-195)	130 (99-191)	129 (87-190)	130 (97-130)	3 months p=0.386 6 months p=0.349
Diastolic BP mmHg	85 (60-105)	78 (54-95)	80 (60-100)	80 (58-103)	79.5 (52-100)	78 (56-120)	3 months p=0.790 6 months p=0.548
TC mmol/l	5.5 (3.4-8.05)	5.3 (3.4-7.25)	4.9 (3.2-8.1)	5.3 (3-7.6)	5.175 (3-8.2)	5.4 (2.9-7.3)	3 months p=0.303 6 months p=0.994
HDL-C mmol/l	1.55 (0.7-2.6)	1.6 (0.5-2.6)	1.6 (0.9-4)	1.5 (0.85-3.3)	1.46 (0.8-2.8)	1.5 (0.9-2.7)	3 months p=0.411 6 months p=0.640
TC: HDL ratio	3.43 (1.8-10.93)	3.39 (1.9-12.4)	3.36 (1.7-6.55)	3.5 (1.52-8.12)	3.52 (1.77-9)	3.23 (2.18-8.11)	3 months p=0.411 6 months p=0.640
Weight kg	66	64.4	65.1	70	70	72.5	3 months p=0.255 6 months p=0.339

mmHg= millimetres of mercury, TC= total cholesterol, HDL-C= HDL-cholesterol, mmol/l= millimol per litre, kg= kilograms, m= metres

Medians (and ranges) shown for BP and cholesterol, medians only for weight

4.6.4. Secondary outcomes

4.6.4.1 Food intake frequency

Data regarding food intake frequency is only available to 3 months. It was identified that consumption of FVL was below the recommended minimum of 5 portions per day (415) in both groups at baseline, Table 4.7. By 3 months this had improved significantly in the intervention group who were attending cooking classes. This group had a significant increase in both fruit and combined FVL consumption (p=0.029 and p=0.016 respectively, Wilcoxon signed-rank test). No such increase was seen in the control group who only received printed information on the benefits of a healthy diet.

The recommended daily intake for females for vitamins A, C and E are 600mcg, 40mg and 3mg respectively (416) (417) (418). The study participant's intake of these vitamins was calculated from the FFQ at baseline and at 3 months, all groups achieved a greater than recommended amount. There was a non-statistical increase in Vitamin A intake in both groups and in Vitamin C intake in the intervention group. The reasons for the small reduction in Vitamin E intake in both groups by 3 months cannot readily be explained; Table 4.8.

Monounsaturated fats are fatty acids which have a single double bond in the fatty acid chain and all of the remaining carbon atoms in the chain are single-bonded. Polyunsaturated fats, by contrast, have more than one double bond. Common monounsaturated fatty acids are palmitoleic acid and oleic acid. Olive oil is approximately 75% monounsaturated fat while lard is approximately 40% monounsaturated fat. Natural sources of monounsaturated fats therefore include olive oil, olive oil based spreads and avocados. The intervention group who were educated on the benefit of olive oil and other related products demonstrated a significant improvement in the ratio of monounsaturated: saturated fat consumption (p=0.022, Wilcoxon signed rank test), Table 4.9, and thereby increased their intake of 'good fats'.

Table 4.7 – Intake of fruit, vegetables and legumes as calculated by FFQ analysis

	Intervention (n=75)			Control (n-55)		
Servings per week	**Baseline**	**3 months**	**Wilcoxon**	**Baseline**	**3 months**	**Wilcoxon**
Vegetables	10.1	11.1	p=0.061	9.6	10.3	p= 0.226
Legumes	2.2	2.2	p=0.976	2.5	2.9	p=0.177
Fruit	11.2	12.7	**p=0.029**	9.1	9.9	p=0.299
Total FVL	23.5	26	**p=0.016**	21.5	23	p=0.84

Medians shown

Table 4.8 – Intake of vitamins A, C and E as calculated by FFQ analysis

	Intervention (n=75)			Control (n-55)		
	Baseline	**3 months**	**Wilcoxon**	**Baseline**	**3 months**	**Wilcoxon**
Vitamin A mcg / day	1108	1246	p=0.101	922	974	p= 0.403
Vitamin C mg / day	94	104	p=0.081	94	94	p=0.929
Vitamin E mg / day	7	6.8	p=0.636	5.8	5.5	p=0.448

mcg= micrograms, mg=milligrams

Medians shown

Table 4.9 – Monounsaturated fat consumption as calculated by FFQ analysis

	Intervention (n=75)			Control (n-55)		
	Baseline	**3 months**	**Wilcoxon**	**Baseline**	**3 months**	**Wilcoxon**
Monounsaturated fats: saturated fats	0.86	0.92	**p=0.022**	0.82	0.83	p= 0.726

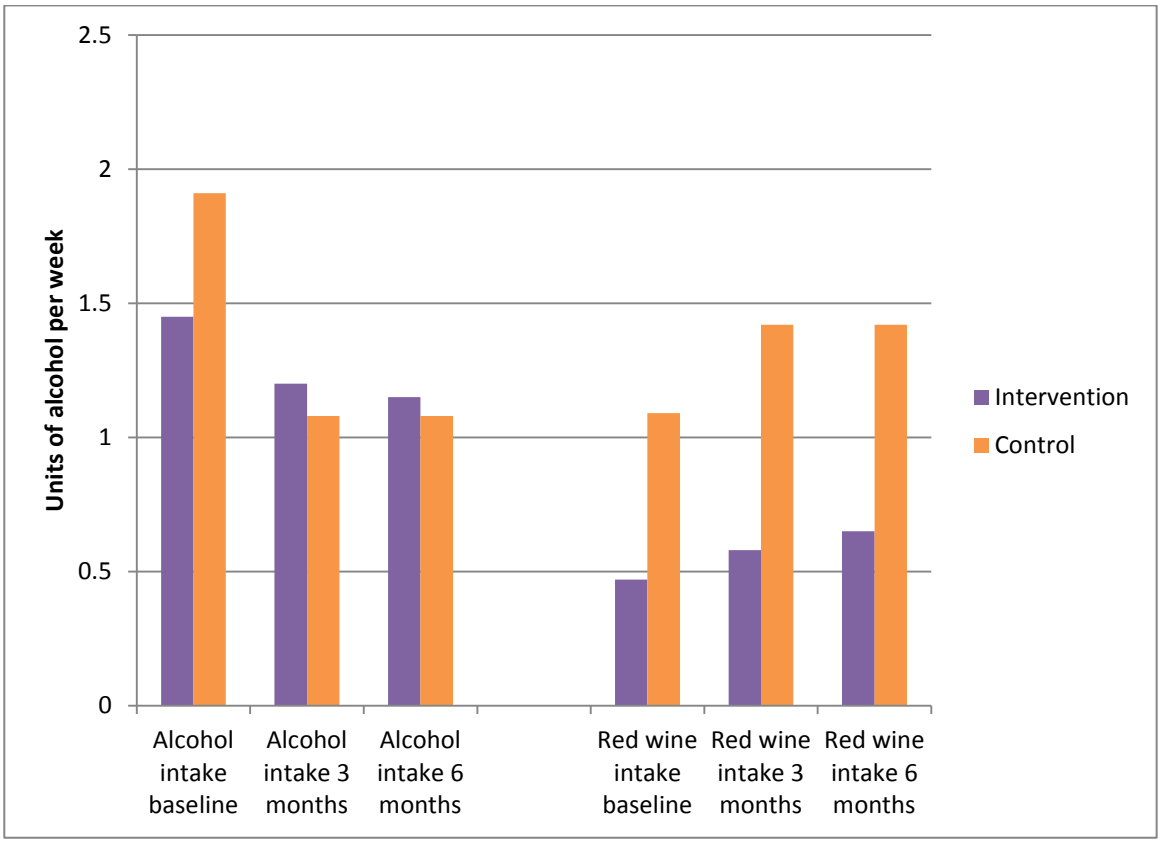
Medians shown

4.6.4.2 Alcohol consumption

In the UK, 1 unit of alcohol is defined as 10ml of pure alcohol (ethanol). Figure 4.2 demonstrates both total alcohol and red wine consumption in both intervention and control groups over the 6 month study period.

Alcohol consumption was low in both groups with a mean consumption of 1.5 units per week in the intervention group and 1.9 units per week in the control group. This tends to be common in females of this age and may also reflect advice given about minimising alcohol intake when taking DMARD therapy (especially when methotrexate is prescribed). Overall alcohol consumption fell slightly in both groups from baseline to 6 months. There was a slight increase in red wine consumption in the intervention group which may reflect the discussions from the cookery course. None of these figures were significant.

Figure 4.2 – Alcohol intake



Medians shown

4.6.4.3 Feedback from participants

All 75 participants in the cookery classes were invited to fill in a questionnaire about their experience of attending the six week cookery course. A total of 57 responses (76%) were received.

The overall consensus was that the classes were very enjoyable. The majority of the participants felt that the recipes given were straightforward to make and affordable. Only 3 respondents stated that they were unable to purchase the necessary ingredients for the recipes used, either because they were too costly or they were unavailable in their local shops. Other positive feedback included benefits from getting out to attend the classes, moving around more and enjoyment from social interaction with other patients with RA. Most individuals had made changes to their diet and approach to cooking. Fifty-three out of the 57 the respondents (93%) had tried the recipes again at home. Most felt they had learnt new skills or tips in preparing and using food. A number reported an increase in confidence and self-esteem.

There was minimal negative feedback on the structure of the courses except for a desire for an opportunity for more time in the cooking class and a longer programme. A number of participants reported a degree of difficulty in preparing some of the ingredients, e.g. vegetables. Ways around this included support from occupational therapy, tutors and from other participants. The use of tinned or frozen ingredients provided an alternative to preparing meals from completely fresh ingredients, Table 4.10 and Figure 4.3.

A short interview was carried out with 3 of the tutors. Attendance at all the courses was high. There was some drop off due to specific reasons, e.g. illness, hospitalisation, holidays. Tutors reported gaining a greater insight and increased awareness of the issues facing individuals with a disability and in particular RA. One felt that it would be useful to know more about the effects of diet on illness and on occasions felt unable to answer some of the more specific questions posed by participants. It was felt that 6 weeks was enough time for the participant to get into a routine.

The pilot project highlighted that within Glasgow there is a shortage of suitable venues and particularly trained tutors to meet the demand for such courses.

In conclusion, both participants and tutors felt that the course had a beneficial effect on individual knowledge and had encouraged the majority of participants to make positive changes to their diet. An equally important message expressed by many of the participants was having the opportunity to socialise and meet with people who faced similar problems, to be able to share experience and information about their illness and to build new friendships.

Table 4.10 – Feedback from cookery courses

Positive feedback	Negative feedback
Enjoyable classes	Unable to purchase ingredients (n=3)
Straightforward recipes	Class too short
Affordable ingredients	Programme too short
Social interaction within classes	Difficulty preparing vegetables
New friendships made	Need for a greater rest period within class
Made changes to diet and approach to cooking	
Learning new food skills	
Improved confidence and self-esteem	

Figure 4.3 – Quotes from cookery course feedback

4.7 DISCUSSION

In this study we sought to assess whether we could modify disease activity and CV risk as well as nutritional patterns in female patients with RA living in areas of social deprivation by introducing them to a Mediterranean-type diet. Cookery classes to provide "hands-on" experience of this type of diet and cooking were an essential element in increasing knowledge and confidence in the participants.

The study has shown that female patients with RA following a Mediterranean-type diet derive modest benefits across a range of areas, suggesting that this type of intervention may be a useful therapeutic adjunct to conventional DMARD which could be popular with patients. While setting up cookery classes and encouraging patients to attend may prove initially difficult to facilitate,

information from the courses could be incorporated into patient information given at diagnosis or on follow-up visits to the out-patient clinic. Issues regarding set up of further dietary programmes are discussed in Section 6.1.3.

4.7.1 Influence on disease activity

Like previous investigators (346), we have shown a modest improvement in a number of measures of disease activity with such a dietary intervention. Pain score was significantly better in the dietary intervention group than in the controls at 3 and 6 months. Patient GH assessment and reported EMS were significantly better at 6 months. Patient function, as reported by the HAQ score, was also better in the intervention group at 3 months. Overall the DAS28 score remained unchanged in both groups, but despite this, patients in the intervention group clearly felt healthier. The reasons for this are likely to be multifactorial and may in part reflect increased confidence and self-esteem as well as the actual dietary intervention. As it is impossible to conduct this type of study in a double-blind fashion, the possibility of a placebo-response cannot be entirely excluded. This does seem less likely as the same trend was seen over a number of measurements and was sustained.

4.7.2 Influence on cardiovascular risk

Patients with RA are at increased risk of CV events and we aimed to assess if we could modify this tendency in our patients. The intervention group lost weight (median 0.9kg over the 6 month period) whereas the control groups showed a weight gain (median 3kg). This difference was however not statistically significant. Cholesterol levels (at baseline and 6 months) and smoking status did not differ between the groups. We noted a small but significant reduction in systolic BP (mean 4mmHg) in the intervention group. The magnitude of change is what perhaps may be achieved with the introduction of a mild anti-hypertensive agent in routine practice. The benefit here is that this was achieved without the addition of any other drugs.

4.7.3 Influence on dietary patterns

The study demonstrates that this intervention was achievable and well received by patients. Intake of fruit, vegetable and legumes increased significantly over 3 months in the intervention group. The use of monounsaturated compared with saturated fats improved. The majority of the participants felt that recipes were straightforward to make and affordable. Only 3 stated that they were unable to purchase the necessary ingredients, either because they were too costly or were unavailable in their local shops. There were also wider social benefits in that most felt they had learnt new skills in food use and preparations. Some women also noted an improvement in confidence and self-esteem as they were now able to contribute more to cooking for themselves and their families at home.

We did not see an improvement in the intake of the antioxidant vitamins A, C and E. Possibly the FFQ was not sufficiently sensitive to detect changes in the actual nutrient intake. The FFQ was originally developed to assess the intake of total energy and macronutrients (protein, fat and carbohydrate) at a time when antioxidants were not the focus of interest (311). The number of fruit and vegetables represented in the FFQ is relatively limited and it is possible that participants increased their intake with items not listed on the FFQ. A more accurate assessment of nutrient intake might have been achieved by using a 7-day weighed or estimated food diary. However, this method places a heavy burden on the participant; this was thought inappropriate for use in this study given the age and health of our subjects. These diaries are expensive and time consuming to analyse; these resources were unavailable to us.

4.8 LIMITATIONS OF THE STUDY

The female-only recruitment policy of this study does raise concerns that the influence of this type of dietary intervention may not be applicable across the spectrum of patients with RA. Unfortunately dietary information was only available to 3 months, while clinical and laboratory parameters were available to 6 months – data on the former would have given valuable information on the longevity of patients adhering to the diet. The availability of weekly courses in a location close to the patients' home and at a convenient time did pose some restriction in allocating participants to intervention or control groups.

4.9 SUMMARY

The initial objectives when designing this study were to assess if lifestyle, disease activity or CV risk might be altered by this type of dietary intervention. The results show that this is indeed achievable at low cost and is acceptable to patients with RA. To act on and implement these findings we have approached local and national (Scottish) public health authorities to inform them of the results and discuss the potential impact of assessment in a larger population.

We disseminated results to other patients attending our general rheumatology clinics. We decided that a simple document, displayed as a poster or given as a hand-out, would convey the results well to those who were interested (Appendix XI).

The then Director of Public Health for NHS Greater Glasgow was informed of the positive outcomes of the study. These were then relayed to the Scottish Diet Co-ordinator in Edinburgh to review the results and assess if applicable to Scotland as a whole.

4.10 ACKNOWLEDGEMENTS

I would like to specifically thank Dr Elaine Morrison, Consultant Rheumatologist, Southern General Hospital and Dr Anne McEntegart, Consultant Rheumatologist, Stobhill Hospital. They have been generous with their time and expertise in the analysis and presentation of the data from this study. Sisters Rosemary Hampson and Geraldine Mackle were integral in patient recruitment and study co-ordination. Ms Ann Tierney was crucial for study administration and later additional statistical support. Sisters Fiona McDonald, Elizabeth McIvor and Audrey Rowan carried out metrology for this study. Mrs Dorothy McKnight provided initial statistical help for this study. The project could not have been completed without the community nutrition tutors. Dr Janet A Scott and students from the Human Nutrition Department of the University of Glasgow provided expert nutritional knowledge and analysis of FFQ.

CHAPTER 5

The Influence of Social Deprivation on Cardiovascular Risk Factor Scores in a Population with Rheumatoid Arthritis

5.1 INTRODUCTION

A risk factor can be defined as characteristic of an individual that is associated with the subsequent development of disease. Risk scores cannot predict absolute risk but are useful for assessing or estimating the possibility of disease; they can also assist in prioritising treatment. Well documented risk factors for CV disease include hypertension, hyperglycaemia and hypercholesterolemia. However, one BP reading is only ever a single snapshot of a fluctuating risk factor; additionally, it is impossible to predict the behaviour of individual atherosclerosclerotic plaques in a patient with hypercholesterolaemia (419).

The standard JBSCRP score and Framingham score for predicting 10-year CV risk have been described earlier (see Section 1.6). The Framingham score was the original CV risk equation, with versions produced in 1991 and 1998 (203, 204). The calculations were based mainly on data from Caucasians living in Massachusetts, USA. In February 2010, NICE withdrew their previous recommendation that the Framingham risk equation should be the equation of choice for assessment of CVD risk, but comment further that it could be considered as a *possible* equation to use (201).

The JBSCRP charts were subsequently based on Framingham and divide by gender, age, smoking and diabetes (420) (see Appendix XII, chart used with permission from the British Medical Journal Publishing Group Ltd). This assessment tool calculates a 10-year risk of all atherosclerotic disease; including acute coronary syndrome, angina pectoris, cerebrovascular disease and peripheral vascular disease. Both JBSCRP and Framingham under-predict in populations with high CHD mortality.

The recent development of the ASSIGN score, based on Scottish population data, allows for the calculation of CV risk with the additional information of family history and deprivation, using SIMD score (205, 206).

5.2 JUSTIFICATION OF STUDY DESIGN AND PROTOCOL

The substantial amount of baseline demographic and CV data collected from the Mediterranean-type diet study of Chapter 4 allowed us to undertake a comprehensive assessment of the influence of social deprivation on CV risk scores in a cohort of female patients with RA living in the Glasgow area.

A comparison of CV risk scores using three different methods (JBSCRP, Framingham and ASSIGN) was undertaken to identify any significant differences in the cohort of female patients with RA recruited to the Mediterranean-type diet study. While the CV risk assessment scores were designed to be used in clinical practice for individuals *without* prior history of hypertension or CV disease, they were applied here to give an indication of risk in this study population.

Baseline CV risk based on BP, age, presence or absence of diabetes and smoking status was calculated using the readily available JBS validated graphs (see Appendix XII, chart used with permission from the British Medical Journal Publishing Group Ltd.) and Framingham calculator (208). Not all of the data required to calculate ASSIGN was collected at study enrolment. Therefore these scores were determined retrospectively. Information regarding SIMD was calculated using the postcode from the address given at study commencement and displayed as part of the ASSIGN score calculator (401). Information on family history of IHD or stroke (in a parent or sibling aged <60 years) was obtained via telephone interview.

5.3 RESULTS

Data was available to allow calculation of CV risk scores in 113 out of 130 participants from the Mediterranean-type diet study (17 participants could not be contacted by telephone resulting in missing data of family history; therefore they were excluded from CV risk analysis using all 3 modalities). All scores were calculated from baseline variables. For the purposes of analysis, risk scores were grouped into 3 sections: (1) <10% 10-year CV risk, (2) 10-20% 10-year CV risk and (3) >20% 10-year risk (as previously detailed in Table 1.10).

None of the recruited patients had a known diagnosis of diabetes mellitus (type I or type II) at time of study enrolment. None had a documented history of MI or stroke.

5.3.1 Comparison of JBSCRP, Framingham and ASSIGN scores in whole cohort

As can be seen from Figure 5.1, JBSCRP was more likely to classify an individual with a <10% 10-year CV disease risk (60.2% of total) than Framingham (50.4% of total) or ASSIGN (47.8% of total). Conversely, ASSIGN was more likely to classify an individual with a >20% 10-year CV disease risk (23% of total) than Framingham (14.2% of total) or JBSCRP (8.8% of total). By using ASSIGN, an additional 16 individuals were identified as having a >20% 10-year CV risk than would have been identified by using traditional JBSCRP. Although the ASSIGN score could still possibly under-estimate, in this cohort it identified additional patients with increased risk. This sub analysis highlights the advantage to our population of using a CV risk score that encompasses family history and deprivation measures.

5.3.2 ASSIGN scores

Table 5.1 documents the demographic and traditional CV risk factors as per ASSIGN 10-year CV risk grouping. A greater predicted CV risk was associated with a higher median SIMD score, which would be expected by the design of the ASSIGN score, and age. This also correlates with a higher median Carstairs grouping for the subsets. Those with an ASSIGN score of <10% 10-year CV risk had a lower median SIMD (25.95, range 2.70-79.83) than in the same grouping of JBSCRP or Framingham.

Figure 5.1 – Outcome of cardiovascular risk calculation using three different scores

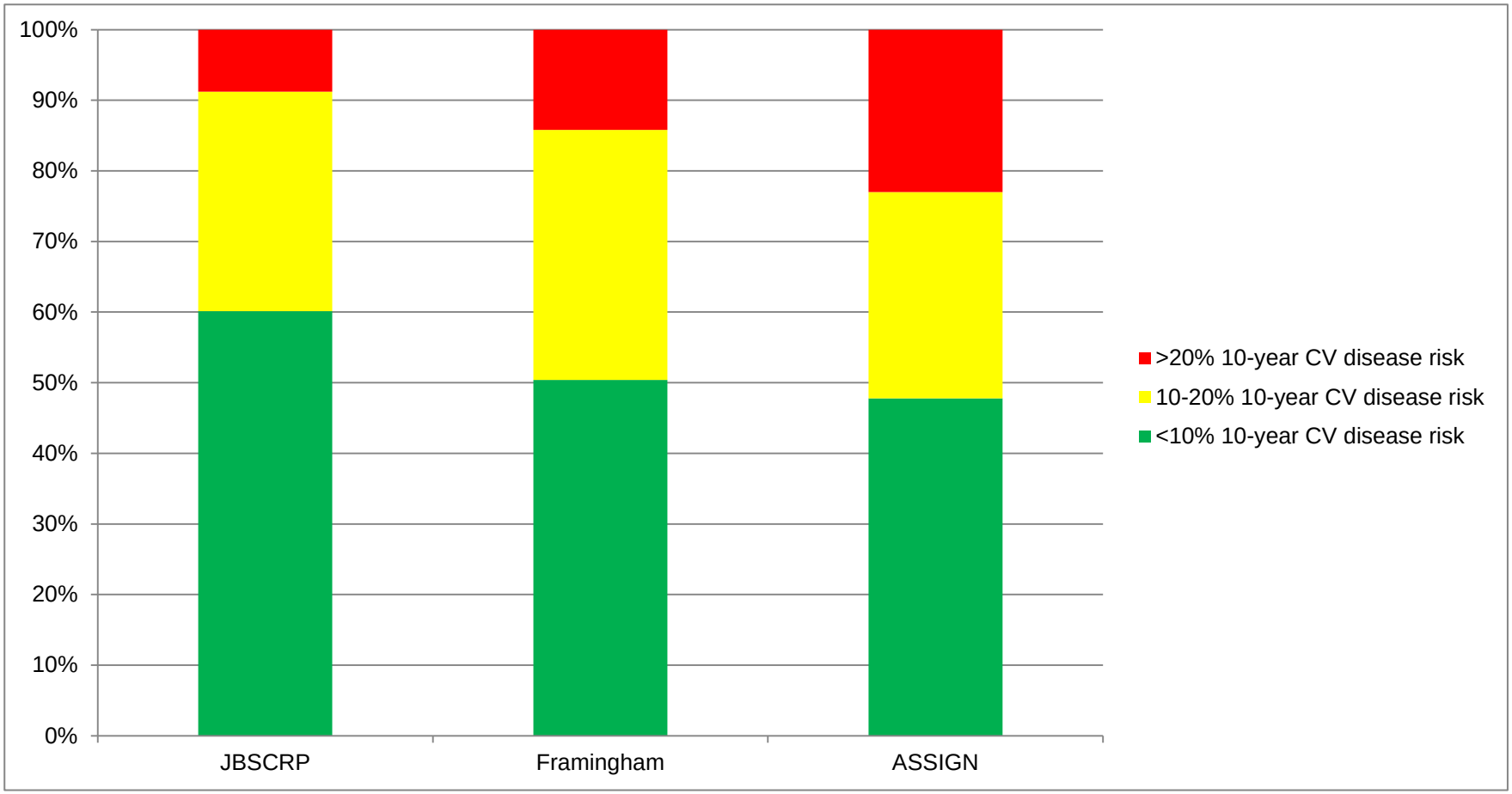


Table 5.1 – Demographic details and traditional CV risk factors as per ASSIGN score

	10-year cardiovascular risk		
	<10% (n=53)	**10-20%** (n=32)	**>20%** (n=28)
Carstairs group	4 (1-7)	5 (1-7)	6 (1-7)
SIMD score	25.95 (2.7-79.83)	42.28 (2.92-77.53)	54.89 (3.08-76.74)
Age years	46 (30-62)	58 (47-71)	65 (55-69)
Systolic BP mmHg	129 (96-191)	137 (111-193)	150 (112-190)
TC mmol/l	5 (3.2-8.05)	5.65 (3.4-7.6)	5.9 (4.75-7.4)
HDL mmol/l	1.62 (0.7-3.3)	1.5 (0.9-2.3)	1.65 (1.2-2.6)
BMI kg/m^2	25.68 (17-47)	28.00 (21-45)	25.96 (18-42)
ESR $mm/1^{st}$ hour	18 (1-46)	19 (1-54)	20 (2-101)
CRP mg/l	7 (6-45)	10 (6-106)	10 (6-132)
Dis. duration years	8 (1-25)	6 (1-39)	8 (1-20)
Ex-smoker	30%	30%	50%
Current smoker	20%	36%	39%
Statin therapy	4%	0	4%
NSAID therapy	76%	73%	65%

Dis. duration = disease duration Medians (and ranges) shown

5.3.3 Discrepancies between calculated cardiovascular risk results

A comparison of whether using the traditional JBSCRP score "matched" the calculated Framingham and ASSIGN score was undertaken. Twenty-four individuals (21% of the cohort) had a Framingham and ASSIGN score which differed from the grouping of the JBSCRP chart. In 15 cases this was when the JBSCRP risk was <10% but both ASSIGN and Framingham calculated a higher risk. In 7 cases this was when the JBSCRP risk was in the grouping 10-20% and both ASSIGN and Framingham calculated a risk >20%.

In 2 cases, JBSCRP gave a higher calculated risk than ASSIGN and Framingham. In the first case, JBSCRP scored a risk of >20%, Framingham 10-20% and ASSIGN <10% (patient number 4 on figure). In the second case, JBSCRP scored a risk of 10-20% and both Framingham and ASSIGN were <10% (patient number 24 on figure), see figure 5.2. Further analysis of these 2 cases did not reveal any striking disease patterns to explain the discrepancy. Both were normotensive, aged ≤40 years, smoked 20 cigarettes per day and had disease durations of ≤4 years. There was, however, a striking disparity in SIMD, DAS28, pain scores and patient GH scores between the 2 patients.

The differences between the groups were interrogated in more detail and are as documented in Table 5.2. The discrepancy was more closely associated with increasing age (median age 63 years in "no match" group, 52 years in "match" group, p=0.001) While the JBSCRP can only give a range of CV risk (i.e. <10%, 10-20% or >20%), ASSIGN and Framingham can give a specific percentage for CV risk over the next 10 years. When JBSCRP matched ASSIGN and Framingham grouping, the median ASSIGN score was 8%; when there was no match, the median ASSIGN score was 19% (p<0.001). A similar pattern was observed with Framingham percentages. This gives weight to the argument that using JBSCRP alone will underestimate CV risk in a proportion of this cohort. There was no significant difference in factors relating to RA control such as ESR or DAS28.

Figure 5.2 – Differing CV risk groupings for individual patients where JBSCRP does not match Framingham or ASSIGN

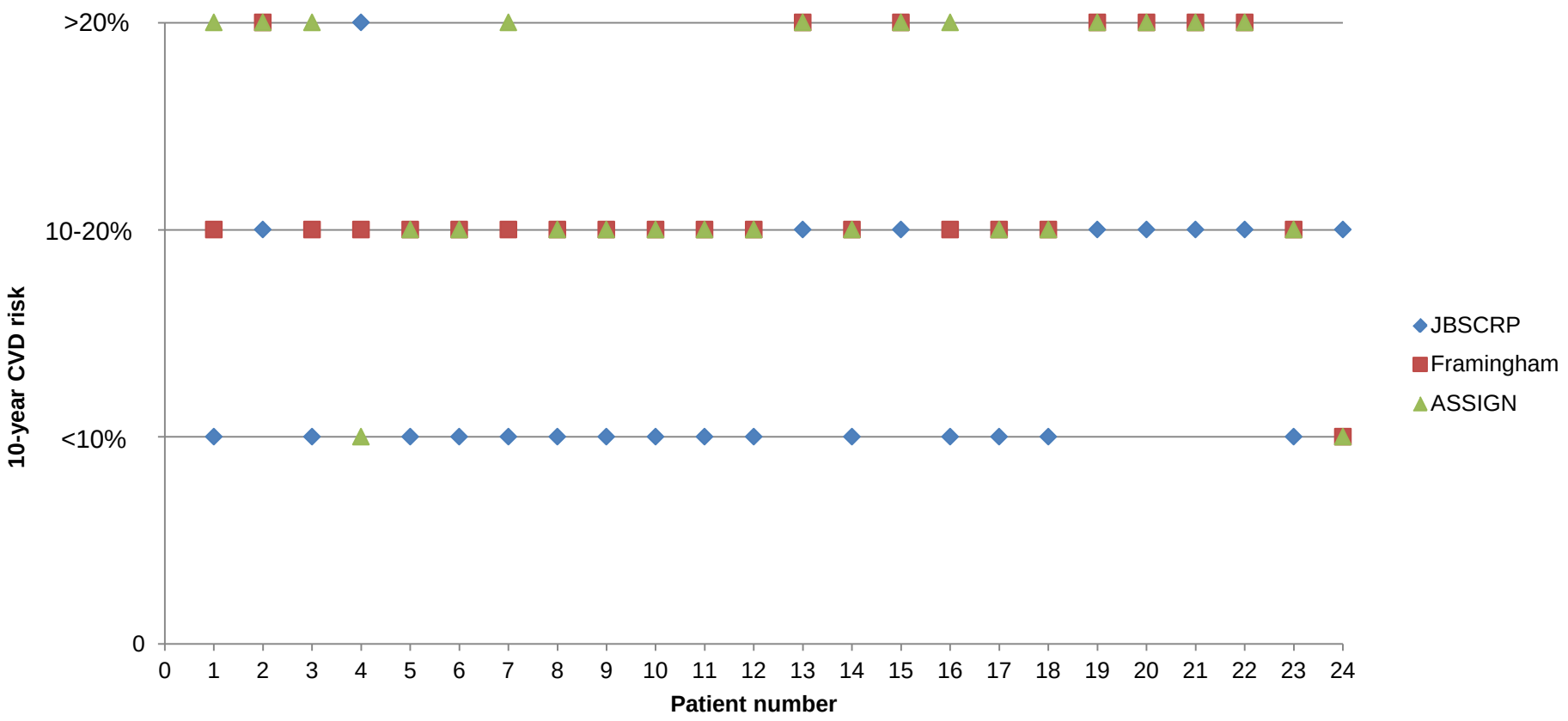


Table 5.2 – Interrogation of patient characteristics comparing a match versus non-match of JBSCRP with ASSIGN and Framingham

	JBSCRP GROUPING DOES NOT MATCH ASSIGN & FRAMINGHAM	JSCRCP GROUPING MATCHES ASSIGN & FRAMINGHAM	
n (%)	24 (21%)	89 (79%)	
Age years	63 (34-71)	52 (30-71)	**p=0.001**
SIMD	49.21 (2.92-79.83)	40.60 (2.70-77.53)	p=0.242
Exact ASSIGN score	19% (8-43)	8% (1-41)	**p<0.001**
Exact Framingham score	12% (9-25)	7% (0-37)	**p=0.003**
DAS28	5.03 (1.5-6.61)	4.59 (1.12-7.13)	p=0.087
ESR mm/1st hour	28 (1-101)	19 (1-69)	**p=0.036**
Systolic BP mmHg	130 (111-177)	134 (96-193)	p=0.070
% smokers	42%	26%	p=0.132

Medians (and ranges) shown

5.4 DISCUSSION

Calculating CV risk is easy to perform with readily available clinical information and at its most accessible form is through the British National Formulary- the JBSCRP charts are at the back of the book (215).

In this analysis, using 3 different CV risk calculations (JBSCRP, Framingham and ASSIGN) the majority of cases will result in identical 10-year CV risk grouping: <10%, 10-20% or >20%. However, 21% of this cohort of 113 female patients with RA had a discrepancy between results. Most commonly this was when JBSCRP scored lower than ASSIGN and / or Framingham. These patients tended to be older ($p=0.001$) and have a higher calculated median ASSIGN score ($p<0.001$). Smoking was more prevalent in these patients. ESR was also higher in the group with discrepancy in CV risk score ($p=0.036$). Additionally, DAS28 was numerical higher in this "non-match" group, but this was not statistically significant.

In 2 cases, however, JBSCRP scored lower than ASSIGN and / or Framingham. Further analysis of these 2 individual cases did not reveal any striking disease patterns to explain the discrepancy.

Interestingly, a low percentage of this cohort were prescribed statins – this was likely because the initial recruitment of the study came at a time where interest in primary and secondary prevention through modulation of lipid levels was just coming to the fore. Additionally, the TARA study, regarding use of statins in RA patients, had just reported in 2004 (128).

5.5 SUMMARY

Review of this cohort demonstrates an increased risk of CVD before the additional risk of RA is taken into account. We have demonstrated that the application of the ASSIGN score in this population provides a more individualised and accurate reflection of CV risk than use of JBSCRP charts alone.

Individuals from deprived socioeconomic groups are clearly at increased CV risk than previously indicated by application of traditional estimating tools. We advocate that the ASSIGN score be used in our population for a more detailed assessment of CV risk; this would be in keeping with the EULAR recommendations for managing CV risk in patients with inflammatory arthritis (153).

CHAPTER 6

Conclusions

6.1 THE ASSESSMENT AND MODIFICATION OF CARDIOVASCULAR RISK IN INFLAMMATORY ARTHRITIS

There is an associated premature mortality associated with RA which is mainly attributable to CVD. It is apparent from the literature that this risk is multifactorial. Potentially modifiable components include manipulation of medication, whose use confers additional risk, as well as addressing issues of smoking, hypertension, poor diet and social deprivation.

The aims of this thesis were to explore the effect of novel interventions on various aspects of RA, predominately to assess CV risk further and review whether certain aspects of risk could be modified.

6.1.1 Cardiovascular risk calculation

The substantial amount of baseline demographic and CV data collected from the Mediterranean-type diet study allowed a comprehensive assessment of the influence of social deprivation on CV risk scores in a cohort of female patients with RA living in the Glasgow area to be undertaken. Three different CV risk calculators were used: Joint British Societies Coronary Risk Prediction, Framingham and the newer, Scottish, ASSIGN score which incorporates social deprivation. ASSIGN was more likely to classify an individual with a >20% 10-year CVD risk (23% of total cohort) than Framingham or JBSCRP. By using ASSIGN, an additional 16 individuals were identified as having a >20% 10-year CV risk than would have been identified by using traditional JBSCRP alone.

I undertook a literature review which could not identify any other published studies which compared different CV risk prediction scores within a cohort of patients with RA or any other disease processes. The authors of the ASSIGN score had proposed a head-to-head comparison with QRISK but the latter study was rapidly published before this could be undertaken (421).

Use of the ASSIGN score allowed the identification of a greater number of study participants with a high 10-year CVD risk score. This was a factor which is addition to the increased CV risk which RA confers. Increased use of this score would allow the targeting of a greater number of patients to target interventions and minimise future CVD.

6.1.2 Manipulation of medication and potential effect on CV risk

The feasibility and effect of anti-inflammatory withdrawal on patients with well-controlled RA was investigated. The initial study proposal was amended after discussion with LREC, and resulted in patients with higher levels of disease activity being excluded. A sudden discontinuation of NSAID was undertaken and 30 patients followed up for 12 weeks. All completed the intervention period with minimal medical intervention – only 11 patients required steroid injections (this comprised 7 IM and 6 IA steroid injections given over a total of 60 follow up visits) and only 1 patient required an escalation of DMARD therapy to maintain good control of their inflammatory disease. None chose to leave the study to restart anti-inflammatory medication. There was no significant deterioration in DAS44 or components by the end of the intervention. There was a trend in reduction of reported upper GI symptoms.

A significant improvement in BP was noted with a maximal median reduction in systolic BP of 7mmHg ($p=0.037$) from baseline to 12 weeks. The relationship between withdrawal of NSAID and reduction in systolic BP remains hypothetical; we cannot exclude that patients became accustomed with the study environment and that this contributed to the sequential fall in BP readings.

The study is limited by its lack of control arm, small size (a larger observational study would have been the preferred option to a blinded trial) and the absence of understanding as to whether the steroid administration or non-NSAID analgesia use represented a change from the norm for each individual patient.

Nevertheless, this was a feasibility study and it is reasonable to expect that these results could be applicable to a larger population. The early increase in pain scores after discontinuing NSAID suggests that a tapered withdrawal might be associated with less discomfort.

This is the first published supportive evidence to implement guidance of limiting NSAID use in patients with RA and low DAS44 scores without adversely affecting quality of life or disease control. The impact this intervention had on BP readings has implications on future CV risk.

6.1.3 Influence of diet on cardiovascular risk in female patients with RA

The impact of a dietary intervention on disease activity and CV parameters was studied in a population of female patients with RA living in areas of socioeconomic deprivation in Glasgow. No other interventions beyond standard care for their arthritis were undertaken. Seventy-five patients were recruited to the intervention group who attended the cookery classes and 55 to the control group who received basic information only. Of the intervention group, 56% were in Carstairs group 6 or 7, being the most deprived.

Comparing intervention with control groups over the 6-month follow up, there was a significant improvement in pain score ($p=0.011$ at 3 months, $p=0.049$ at 6 months), in functional assessment (reduction in HAQ score at 6 months, $p=0.03$) and in EMS ($p=0.041$ at 6months). The intervention group demonstrated a benefit in systolic BP. There was no significant reduction in inflammatory markers. There was a significant increase in fruit and vegetable consumption as assessed by food frequency questionnaire.

This study demonstrated that a cheap and easily delivered 6-week intervention can prove instrumental in increasing a cohort's intake of healthy foods with the subsequent potential health benefits, including impact on CVD. The study was however limited to 75 patients, and the majority had similar social circumstances.

This type of intervention has potential public health implications. The results were disseminated to the Director of Public Health in Glasgow and subsequently to the Scottish Diet Co-ordinator in Edinburgh. After the paper relating to this work was published, much interest was generated by health and diet related websites and forums, indicating the general population's interest in dietary interventions.

Information on diet is available from charitable resources to aid patients and carers make healthy eating choices. Arthritis Research UK entitle their booklet "Diet and Arthritis" and comment on a number of important issues highlighted in the Introduction of this thesis, such as: maintaining a healthy weight, mono-unsaturated versus polyunsaturated fats, fish oil supplements and interestingly, the most recent version details "the potential benefits of a Mediterranean style diet" (422). Arthritis Care entitle their booklet "Healthy Eating and Arthritis"

(423) and details controlling weight as well as tips on maintaining a healthy diet (e.g. planning shopping trips, storing healthy food in the freezer, organising the kitchen to make food preparation easier). Fish oils and fish liver oils are discussed. Uniquely, advice is given on avoiding unpasteurised cheese and milk and uncooked meats if taking immunosuppressant therapy.

6.2 FUTURE WORK

On the basis of the work reported in this thesis, areas have been highlighted which warrant further assessment.

6.2.1 Anti-inflammatory use

On a day-to-day basis this research work has informed my daily practice in a rheumatology out-patient clinic, and hopefully that of my co-workers. I will continue to strive to address anti-inflammatory use in all patients with inflammatory arthritis that I see, in order to ensure that the risk versus benefit ratio of such therapy is at the forefront of discussion. The result of the work reported in the thesis is simple to convey to patients: participants with good control of their arthritis were able to safely withdraw anti-inflammatory drug use without significant flare of their disease and with major potential health benefits such as reduction in BP and upper GI symptoms.

From a clinical study perspective, the monitoring of a larger group over a more prolonged period would undoubtedly give a more robust understanding on the effect of the intervention on BP as well as monitoring disease activity. hsCRP, specific circulating cytokines or thrombotic variables (such as fibrinogen, von Willebrand factor or D-dimers) could potentially be monitored in a larger study. A further question that could be answered by more research in this area is, if NSAID were to be re-introduced at a later stage, what might the effect be on BP and pain score?

The fact that minimal medical intervention was required should give reassurance that the amount of extra resources needed would likely be small. Extending such a study to other patients with higher levels of disease activity and including types of inflammatory pathologies such as PsA and / or AS would be helpful. The documented tolerance of such an intervention by patients would

hopefully encourage any future Ethics Committee review that this is an achievable target to minimise CV, GI and renal complications in patients with inflammatory arthritis.

6.2.2 Dietary intervention

Firstly, this study informs daily practice when engaging with patients on the topic of self-management of their RA: advising on a healthy diet can make an impact on general health and well-being as potentially acting as an adjunct to RA disease control and reducing CV risk.

Additional clinical research work developing on from this Mediterranean-type diet would be extremely useful. There is scope to extend the project out to involve males (with the potential need to address the issue of how to make this an attractive study to them) and other types of inflammatory pathology or even connective diseases; systemic lupus erythematous is also associated with increased CV risk. Having a larger number of study participants and a wider socioeconomic mix would prove that the results were also applicable to the wider RA population. Laboratory based work could potentially explore the impact of dietary intervention on endothelial function, arterial stiffness and provide further information on thrombotic variables and anti-oxidants.

The question then arises of how best to implement such dietary changes in the RA population. A number of publications have detailed the benefit of medical student-led teaching in an undergraduate setting (424); such a peer-supported process could be applied to the teaching of nutritional and cooking skills by patients with RA to others with the condition. This could perhaps be done in conjunction with arthritis patient support groups, with training put in place for the 'tutors'. This would potentially allow further implementation of such a diet in a community setting.

Hand function in relation to ability to undertake food preparation and cooking was not taken into account within inclusion or exclusion criteria for this diet study. Occupational Therapy staff at the 3 recruiting hospital advised on the provision of aids for food preparation where necessary, although the data relating to how much input was required is not available. It is perhaps reasonable to think that any further dietary study of this nature may wish to specifically take hand function into account as part of recruitment into a dietary

study; a patient with poor hand function may find such an intervention difficult to undertake and subsequently have worse outcomes.

Most functional scales for assessing disability in the rheumatoid hand use standardised tasks required specialist equipment, trained personnel or both; they are often complicated for routine use. A more amenable assessment which could be used is the Cochin Scale (425). This comprises 18 questions concerning activities of daily living graded from 0 (performed without difficulty) to 5 (impossible to do), giving a disability score out of 90. It only takes 3-4 minutes to perform and can be done without equipment or trained physicians. On reflection, use of the Cochin Scale in this study would have been feasible to undertake at time of study recruitment and could be used in further research work of this nature.

6.2.3 Cardiovascular risk assessment

If patients were to have specific CV risk calculations carried out on a regular basis in the rheumatology out-patient clinic, this would adhere to the EULAR recommendations outlined in Section1.4.10 and allow interventions to be targeted where needed. This means that close monitoring of BP and lipid levels need to be performed in the clinic or done in conjunction with the patient's GP surgery.

Ideally, patients who have a full CV risk assessment carried out could be monitored over time to assess if MI or stroke has occurred. While this may be difficult in routine practice due to numbers involved, it is possible that patients starting anti-TNF or other biologic therapy could be followed up more easily, due to the often frequent and specialist nature of their subsequent reviews. The ASSIGN score would be the appropriate assessment of CV risk in the recruiting rheumatology unit, as it takes into account social deprivation.

APPENDICES

APPENDIX I - SAMPLE PAGE FROM FOOD FREQUENCY QUESTIONNAIRE

Please ensure you have a tick (☑) on every line Adapted from (311)

FOODS & AMOUNTS	AVERAGE USE							
	Never / less than 1 per month	1-3 per month	Once per week	2-4 per week	5-6 per week	Daily	4-5 per day	6+ per day
DRINKS								
Tea - cup								
Coffee (instant/ground) - cup								
Coffee (decaffeinated) – cup								
Cocoa / hot chocolate – cup								
Horlicks / Ovaltine – cup								
Wine – glass								
Beer / lager / cider – half pint								
Port / sherry / liqueur – glass								
Spirits (gin / vodka / whisky) – glass								
Low calorie / diet fizzy drink – glass								
Fizzy soft drink – glass								
100% pure fruit juice – glass								
Fruit squash / cordial – glass								
FRUIT								
Apples								
Pear s								
Oranges / Satsumas / mandarin s								
Grapefruits								
Bananas								
Grapes								
Melon								
Peaches / plums / apricots								
Strawberries / raspberries / kiwi								
Tinned fruit								
Dried fruit (raisins / prunes)								

APPENDIX II – NSAID WITHDRAWAL STUDY PATIENT RECRUITMENT POSTER

DO YOU HAVE RHEUMATOID ARTHRITIS?
ARE YOU ON A NON-STEROIDAL ANTI-INFLAMMATORY DRUG?

Eg. ibuprofen / Nurofen
dclofenac / Voltarol
naproxen / Naprosyn
etodolac / Lodine

WOULD YOU LIKE TO TRY STOPPING YOUR ANTI-INFLAMMATORY TABLETS FOR A PERIOD OF TIME?

HERE AT THE ROYAL INFIRMARY WE'RE DOING A STUDY WHERE VOLUNTEERS COME OFF THEIR ANTI-INFLAMMATORY TABLETS AND WE MONITOR THEM CLOSELY TO SEE WHAT HAPPENS

IF YOUR JOINTS WERE TO BECOME MORE PAINFUL WE WOULD LOOK AT *OTHER* WAYS OF IMPROVING THINGS

IF YOU ARE INTERESTED IN HELPING US, PLEASE SPEAK TO ONE OF THE DOCTORS OR NURSES AT THE CLINIC TODAY

Thank you

POSTER VERSION 1.0
08/08/2006

APPENDIX III – NSAID WITHDRAWAL STUDY PATIENT INFORMATION SHEET

PATIENT INFORMATION SHEET

A PILOT STUDY TO ESTABLISH IF IT IS POSSIBLE TO WITHDRAW NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) FROM PATIENTS WITH RHEUMATOID ARTHRITIS (RA)

You are being invited to take part in a research study which is investigating whether withdrawing non-steroidal anti-inflammatory drugs will alter the way your joints feel or lower your blood pressure. Before you decide, it is important for you to understand why the research is being done and what it will involve.

Please take time to read the following information carefully and discuss it friends, relatives or your GP if you wish. It tells you about the study and will answer some questions that you may have. Please ask us if there is anything that is not clear or if you would like more information. We want to be sure that you understand what the study is about. A leaflet entitled 'Medical Research and You' which gives information about medical research is available from Consumers for Ethics Research (CERES). If you would like a copy, please ask us for one.

Please take some time to decide whether or not you wish to take part in this study. Thank you very much for reading this.

What is the purpose of the study?
Many people take non-steroidal anti-inflammatory drugs (NSAIDs) every day for their rheumatoid arthritis (RA). Examples of these tablets include: ibuprofen (Brufen), diclofenac (Voltarol) and etodolac (Lodine). Recent studies have shown that regular use of this type of drug may cause a slight rise in blood pressure or cause symptoms such as heartburn. We would like to see what happens to your symptoms of arthritis and blood pressure if we withdraw these drugs in a controlled manner. If we think that your RA has flared up as a result of this change, we have a programme to alter your other drugs / inject the troublesome joints.

Why have I been chosen?
You have been chosen because you have RA, and are currently being prescribed a NSAID as part of your treatment for this. This study is taking place at Glasgow Royal Infirmary and at Stobhill Hospital. We aim to recruit a total of 30 patients into this study.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
If you are suitable for the study and are happy to take part, you will begin by signing an

informed consent form. You will be given a copy of the information sheet and the signed consent form to keep. You will then attend a screening visit which will assess your eligibility for the study in more detail. If after this you fit the eligibility criteria and are still happy to take part, you will enter the study and be asked to stop taking your NSAID.

We will ask you to *completely* stop taking NSAIDs from the time you enter our study - we do *not* wish you to gradually reduce the dose as this may cause confusion with interpreting the results of the study. We will ask your general practitioner (GP) by letter not to prescribe any NSAIDs while you are participating in this study and kindly ask that you do *not* take NSAIDs that have been bought over-the-counter from a pharmacy.

You will still take other medicines prescribed for your RA (eg. Sulphasalazine, Hydroxychloroquine or Methotrexate) and you will still be allowed to take other painkillers such as Paracetamol or Co-Codamol. Your involvement in the study will last for 12 weeks and you will need to make 3 visits to hospital. At the end of these visits you will be followed up at a routine rheumatology out patient appointment.

What do I have to do?

Baseline visit	After you have given written, fully informed consent, your study doctor or nurse will assess your arthritis by counting your tender and swollen joints and asking you to complete some questionnaires. Your blood pressure will be measured three times and we will record the average of these measurements. A blood sample (about 20ml or about 4 teaspoons full) will be taken and sent for laboratory testing to measure the levels of inflammatory proteins in your blood. These may be higher than normal because of your rheumatoid arthritis. Details of your medications will be recorded. We'll also record your weight, height, waist and hip measurements. You will be given a diary where we will ask you to record the days on which you may have had to take extra pain-killers.
Visit 2 (week 6)	Your study doctor or nurse will assess your arthritis by counting your tender and swollen joints and asking you to complete some questionnaires. Your blood pressure will be measured three times and we will record the average of these measurements. A blood sample (about 20ml or about 4 teaspoons full) will be taken and sent for laboratory testing to measure the levels of inflammatory proteins in your blood related to your rheumatoid arthritis. Details of your medications will be recorded and any additional, supporting medication you are taking will also be noted. We will review your diary where you may have marked when you have had to take extra pain-killers.

Visit 3 (week 12)	Your study doctor or nurse will assess your arthritis by counting your tender and swollen joints and asking you to complete some questionnaires. Your blood pressure will be measured three times and we will record the average of these measurements. A blood sample (about 20ml or about 4 teaspoons full) will be taken and sent for laboratory testing to measure the levels of inflammatory proteins in your blood related to your rheumatoid arthritis. Details of your medications will be recorded and any additional, supporting medication you are taking will also be noted. We'll also record your weight. We will review your diary where you may have marked when you have had to take extra pain-killers.

What are the alternatives to taking part in this study?
Currently, the recommended standard of care is that you continue receiving medications which your GP and rheumatologist have advised. If you decide not to take part you will continue to receive the best standard of care available at the hospital. The standard of care will not be affected in any way if you decide not to take part.

What are the risks of the study?
The main concern would be that you would feel your joints a bit stiffer or your RA would flare after stopping taking the NSAIDs. This is the main reason for monitoring you closely in the study - we would wish to act quickly and try additional methods to ease your joint pain.

Are there any benefits to taking part in the study?
We hope that you may experience an improvement in your blood pressure but we cannot guarantee this and you may experience no benefits at all. In addition, you may feel less gastro-intestinal side-effects off these drugs. By taking part, however, you will be helping to provide information that may assist others with rheumatoid arthritis in the future.

What if new information becomes available?
Sometimes during the course of a research project, new information becomes available. If this happens, you will receive the information in writing. This may change the way you feel about taking part in the study and you are free to withdraw at any time. If you decide to withdraw, your study doctor will make arrangements for alternative care. If you decide to remain in the study you will be asked to sign an updated consent form to confirm that this new information has been explained to you.

Also, on receiving new information your doctor might consider it to be in your best interests to withdraw you from the study. They will explain the reasons and arrange for your care to continue.

What happens at the end of the study?
You will continue with your normal hospital treatment, medication and care as your rheumatologist advises. We will send you a letter to inform you of the study's overall results.

What if I want to stop taking part in this study?
Your participation is completely voluntary and you can decide not to take part in the study at any time. This will not affect your care in any way, either now or in the future. If your personal circumstances change and you no longer wish to be involved you may leave at any time. You do not have to give a reason and this will not affect how your doctor cares for you. If at any time you decide to stop taking part in the study, you should inform the study doctor. Your study doctor may ask you for the reason you wish to stop participating but you should not feel that you have to tell him/her.

What happens if something goes wrong?
The sponsor of this study, Glasgow Royal Infirmary has insurance which covers legal liability for any injuries caused to trial participants arising out of this research. If you are harmed due to someone's negligence, then you may have grounds for legal action. Regardless of this, if you have cause to complain about any aspect of the way you have been approached or treated during this study, then normal National Health Service complaint mechanisms are available to you.

What about confidentiality?
If you wish to take part in the study we will let your GP know, with your consent. In addition, we will ask your GP to let us know of any *relevant* medical problems that we may not know about. This would only be in relation to any problems that could influence how we interpret the results of this study and would again only be done with your consent.

Members of the research team from the Glasgow Royal Infirmary/Stobhill Hospital will need to inspect your health records, relevant to this study. In certain circumstances your records or results may be looked at by members of appropriate regulatory bodies, for purposes of checking that the study is being done correctly. By signing the consent form, you are agreeing to let these people see your medical notes. Confidentiality is promised in all cases and your identity and address will not be disclosed. Any information that may leave the hospital, apart from that we send to your GP, will have your name and address removed and you will only be identified by your initials and study number. You will not be identified in any report/publication resulting from the research. Under the UK Data Protection Act (1998), you may ask to see your study records. Coded data about you collected during the study will be stored on password protected computerised systems for the purpose of processing, analysis, etc. by authorised study personnel.

Who is organising and funding the research?
The Centre for Rheumatic Diseases is organising this research study. The research is being sponsored by Glasgow Royal Infirmary and is being supported in part by an educational scholarship from the Royal College of Physicians & Surgeons in Glasgow, which is contributing to the salary of Dr Gayle McKellar The study objectives and its proposed conduct has been reviewed by the Glasgow Royal Infirmary Research Ethics Committee and has given approval for the study on 18th September 2006.

What will happen to the results of the research study?
The results of this study will be part of work that will be published in scientific and/or medical journals. You will not be identified in any paper or publication. In addition, the results of this study may form part of a submission for a higher degree for Dr Gayle McKellar.

Who do I call if I have any questions or problems?
Please contact the study doctor or nurse below at any time, if you would like more information about any part of this study or if you would like more information about what to do in case of a study related injury or receive a copy of Consumers for Ethics Research (CERES)

Contact names and numbers
If you need any further information please do not hesitate to contact Dr Gayle McKellar, Professor Hilary Capell and Dr Rajan Madhok (Glasgow Royal Infirmary) or Dr Anne McEntegart and Dr Hilary Wilson (Stobhill Hospital). You should also contact your GP for independent advice should you so desire.

Dr Gayle McKellar	**Tel: 0141 211 4000 (page 1106)**
Professor Hilary Capell	**Tel: 0141 211 4965**
Dr Rajan Madhok	**Tel: 0141 211 4966**
Dr Anne McEntegart	**Tel: 0141 211 3306**
Dr Hilary Wilson	**Tel: 0141 211 3306**
Sister Rosie Hampson	**Tel: 0141 211 4408**

APPENDIX IV – NSAID WITHDRAWAL STUDY CONSENT FORM

A PILOT STUDY TO ESTABLISH IF IT IS POSSIBLE TO WITHDRAW NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) FROM PATIENTS WITH RHEUMATOID ARTHRITIS (RA)

Chief Investigator: Dr Gayle McKellar

Centre for Rheumatic Diseases, Glasgow Royal Infirmary, 84 Castle Street, Glasgow, G4 0SF

INFORMED CONSENT FORM

Please read the following statements and initial the box beside the statement if you agree with it.

1. I confirm that I have read and understand the information sheet dated 12.09.06 (version 2.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	
3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4. I agree to my GP being informed of my participation in the study and being asked to provide any information relevant to this study that we may not be aware of.	
5. I agree to take part in the above study.	

_____	_____	_____
Name of Patient	**Date**	**Signature**
_____	_____	_____
Name of Person taking consent	**Date**	**Signature**

When completed –

1 copy for patient, 1 copy for researcher site file, 1 copy (original) to be kept in medical notes

APPENDIX V – MEDITERRANEAN-TYPE DIET PATIENT INFORMATION SHEET

PATIENT INFORMATION SHEET

A PILOT STUDY OF THE EFFECT OF MEDITERRANEAN DIET INTERVENTION ON DISEASE ACTIVITY AND HAEMATOLOGICAL MARKERS OF CARDIOVASCULAR RISK IN FEMALE PATIENTS WITH RHEUMATOID ARTHRITIS (RA)

Lay Title: Does changing to a Mediterranean Diet alter blood markers of cardiovascular risk and rheumatoid arthritis activity in female patients with Rheumatoid Arthritis?

We would like to invite you to help with the above research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study? A recent Swedish study showed that taking a Mediterranean-type diet (ie. high in vegetables, fruits, nuts, beans, pulses and fish but low in meat and high-fat dairy products) was helpful to patients with rheumatoid arthritis in reducing joint inflammation and in improving physical function and energy levels. We would like to study whether the same is true in Glasgow patients as this might prove a useful form of therapy in addition to currently available treatments.

The Mediterranean Diet also benefits health in other ways and is associated with lower levels of heart disease. We also plan to study and measure some aspects of this.

Why have I been chosen? We are inviting 180 female patients with rheumatoid arthritis attending the rheumatology clinics at the Southern General Hospital, Glasgow Royal Infirmary and Stobhill Hospital to take part in the study (60 patients at each hospital).

Do I have to take part? It is up to you to decide whether or not to take part. If you do wish to take part you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision not to take part, or a decision to withdraw at any time, will not affect the standard of care you receive.

What will happen to me if I decide to take part? We are comparing the effects of the Mediterranean diet with an ordinary diet. Patients will be allocated at random to either the treatment group (Mediterranean Diet) or control group (ordinary diet).

The study will last for 6 months.

If you are allocated to the Mediterranean diet group you will be asked to do the following :

1. Attend a "Get Cooking, Get Shopping" course run by nutrition (food) specialists and organised by the Health Promotion Department of Greater Glasgow Health Board. The course is free and will provide you with all the information you need about the Mediterranean Diet to allow you to change your current diet to a healthier diet in the long term. It involves one two hour session per week for 6 weeks and you will be able to take part in cooking as well as discussion and will be given some written information. The course will be held locally and will involve 10 people at a time.

2. Attend the hospital on 4 occasions (at the start of the study, after two weeks, 3 months & 6 months) for assessment by a nurse. At the screening visit the study will be explained again and you will be issued with a food diary to record your food intake and be shown how to complete the diary. At each subsequent visit the activity of your arthritis will be assessed, you will be asked to complete a health assessment questionnaire, your weight will be checked and the nurse will go over your food diary.

   In addition, a blood sample (25mls = 1 & ¾ tablespoonful in total) will be taken to check the ESR and CRP (markers of the inflammation associated with arthritis), FRAP test (a marker of fruit and vegetable intake), thrombotic or "clotting" test (markers of heart disease risk) and lipid (blood fat) levels.

3. A note will be made of any other illnesses you have and of the medications you are taking.

4. Smoking history and alcohol intake will also be noted.

If you are allocated to the ordinary diet group:

At the screening visit the study will be explained again and you will be issued with a food diary to record your food intake and be shown how to complete the diary. You will be given written information about healthy eating but will not attend the "Get Cooking, Get Shopping" course. You will be asked to attend for the same assessments at the hospital outlined above.

(NB. You will be offered delayed entry into the Mediterranean Diet part of the study at a later date if you wish.).

Will my usual arthritis treatment be affected? No. Your medications and other treatments (eg. physiotherapy, occupational therapy) will stay the same. However, we would like, if possible, to avoid steroid injections (into the joints or muscles) within 4 weeks of an assessment.

What are the possible risks of taking part? There are no known risks associated with taking part in the study. A healthy diet is likely to prove beneficial to general health.

What are the possible benefits? We hope that the Mediterranean Diet will help rheumatoid arthritis. However, this cannot be guaranteed. The information we get from the study may help us with the future treatment of patients with rheumatoid arthritis.

Will my taking part in this study be kept confidential? Yes. All information which is collected about you during the course of the study will be kept confidential.

What will happen to the results of the research study? Once all of the results have been analysed we may seek to publish them in an anonymous format in a medical journal. There are no immediate plans to link this piece of research with other research ongoing within our department. However it is possible that this may be considered in the future and you should be aware that the information gathered during this study may be held indefinitely and linked anonymously to other pieces of research in the future.

Who has reviewed the study? Members of the Local Research Ethics Committee at Glasgow Royal Infirmary have reviewed the study.

Who do I contact for further information about this study? Thank you for taking the time to read this information sheet. If you have any concerns or questions about the study at any time you can discuss these with the study team

Doctor:	Hilary Capell	Telephone: 0141-211-4965
Sister:	Rosie Hampson	Telephone: 0141-211-4408

APPENDIX VI – MEDITERRANEAN-TYPE DIET STUDY CONSENT FORM

A PILOT STUDY OF THE EFFECT OF MEDITERRANEAN DIET INTERVENTION ON DISEASE ACTIVITY AND HAEMATOLOGICAL MARKERS OF CARDIOVASCULAR RISK IN FEMALE PATIENTS WITH RHEUMATOID ARTHRITIS (RA)

Lay Title: Does changing to a Mediterranean Diet alter blood markers of cardiovascular risk and rheumatoid arthritis activity in female patients with Rheumatoid Arthritis?

Chief Investigator: Dr Hilary A Capell

Centre for Rheumatic Diseases, Glasgow Royal Infirmary, 84 Castle Street, Glasgow, G4 0SF

INFORMED CONSENT FORM

Please read the following statements and initial the box beside the statement if you agree with it.

1. I confirm that I have read and understood the Patient Information Sheet dated September 2003 (version 2) for the above study and have had the opportunity to ask questions	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3. I agree to take part in the above study.	

_____	_____	_____
Name of Patient	**Date**	**Signature**
_____	_____	_____
Name of Person taking consent	**Date**	**Signature**

APPENDIX VII – SAMPLE SF-12 FORM Adapted from (395)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

Excellent ◯ Very good ◯ Good ◯ Fair ◯ Poor ◯

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not at all limited
Moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf?	◯	◯	◯
Climbing several flights of stairs?	◯	◯	◯

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	Never
Accomplished less than you would have liked	◯	◯	◯	◯	◯
Were limited in the kind of work or activities	◯	◯	◯	◯	◯

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious?)

	All of the time	Most of the time	Some of the time	A little of the time	Never
Accomplished less than you would have liked	◯	◯	◯	◯	◯
Limited in the kind of work / activities	◯	◯	◯	◯	◯

5. During the past 4 weeks, how much did pain interfere with your normal work (including work outside the home and housework)?

Not at all ◯ A little bit ◯ Moderately ◯ Quite a bit ◯ Extremely ◯

6. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Have you felt calm and peaceful	◯	◯	◯	◯	◯
Did you have a lot of energy	◯	◯	◯	◯	◯
Have you felt downhearted and depressed	◯	◯	◯	◯	◯

7. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends and family) etc?**

All of the time ◯ Most of the time ◯ Some of the time ◯ A little of the time ◯ None of the time ◯

APPENDIX VIII – SAMPLE HAQ FORM Adapted from (399)

Please place an "X" in the box which best describes your abilities over the last week

	Without any difficulty	With some difficulty	With much difficulty	Unable to do
DRESSING & GROOMING				
Are you able to:	○	○	○	○
Dress yourself, including shoelaces and buttons?				
Shampoo your hair?	○	○	○	○
ARISING				
Are you able to:	○	○	○	○
Stand up from a straight chair?				
Get in and out of bed?	○	○	○	○
EATING				
Are you able to:	○	○	○	○
Cut your own meat?				
Lift a full cup or glass to your mouth?	○	○	○	○
Open a new milk carton?	○	○	○	○
WALKING				
Are you able to:	○	○	○	○
Walk outdoors on flat ground?				
Climb up five steps?	○	○	○	○

Please mark any AIDS or DEVICES that you usually use for any of the above activities:

Devices used for dressing ○ Built up or special utensils ○ Crutches ○
Walking stick ○ Wheelchair ○ Zimmer / frame ○
Special / built up chair ○

Please mark any categories for which you usually need HELP FROM ANOTHER PERSON:

Dressing and grooming ○ Arising ○ Eating ○ Walking ○

Please rate HOW WELL YOU ARE on a scale of zero to 100 | | | |

How much PAIN have you had in the PAST WEEK on a scale of zero to 100 | | | |

Please place an "X" in the box which best describes your abilities over the last week

	Without any difficulty	With some difficulty	With much difficulty	Unable to do
HYGIENE				
Are you able to:	◯	◯	◯	◯
Wash and dry your body?				
Take a tub bath?	◯	◯	◯	◯
Get on and off the toilet?	◯	◯	◯	◯
REACH				
Are you able to:	◯	◯	◯	◯
Reach and get a bag of sugar from above your head?				
Bend down to pick something off the floor?	◯	◯	◯	◯
GRIP				
Are you able to:	◯	◯	◯	◯
Open car doors?				
Open previously opened jars?	◯	◯	◯	◯
Turn taps on and off?	◯	◯	◯	◯
ACTIVITIES				
Are you able to:	◯	◯	◯	◯
Run errands and shop?				
Get in and out of a car?	◯	◯	◯	◯
Do household chores like vacuuming?	◯	◯	◯	◯

Please mark any AIDS or DEVICES that you usually use for any of the above activities:

Raised toilet seat ◯ Bath handles ◯ Bath seat ◯
Long handled appliances for reach ◯ Long handled appliances in bathroom ◯ Jar opener (for jars previously opened) ◯

Please mark any categories for which you usually need HELP FROM ANOTHER PERSON:

Hygiene ◯ Reach ◯ Gripping and opening things ◯ Errands and chores ◯

To what extent are you able to carry out your EVERYDAY PHYSICAL ACTIVITIES such as walking, climbing stairs, carrying groceries or moving a chair?

Completely ◯ Mostly ◯ Moderately ◯ A little ◯ Not at all ◯

APPENDIX IX – HEALTHY EATING INFORMATION SHEET

Some suggestions for:

BREAKFAST
High fibre cereal and semi-skimmed milk
Muesli and low fat yoghurt
Wholemeal toast and a little butter or margarine
Wholemeal toast and banana


SNACK MEALS
Beans on toast
Wholemeal bread sandwich with salad and cold meat, sardines, cheese, egg or chicken
Edam and tomato toastie
Baked potato with tuna and corn
Home made lentil soup and crusty bread

MAIN MEALS
Lean mince, carrots, boiled potatoes
Spaghetti Bolognaise and salad
Baked chicken with baked potato and green vegetables
Grilled fish fingers, tomato and potatoes
Lentil curry with wholemeal chappatis




PUDDINGS
Fresh/dried fruit salad
Milk pudding and stewed or tinned fruit
Low fat fruit yoghurt
Banana and low fat Fromage Frais

Staying on a Healthy Diet

Choose a wide variety of fruit and vegetables
Base all meals on starchy foods such as bread, potatoes and cereals
Choose low fat versions of milk and dairy foods
Vary main courses to include fish (particularly oily types), poultry, lean meat, beans and pulses
Eat fatty and sugary foods only occasionally and in small amounts

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The Balance for Health

A Guide to Healthy Eating for Adults

Healthy eating depends on having a variety of foods from the four main food groups

- **Bread and Cereals**
- **Fruit and Vegetables**
- **Meat and Alternatives**
- **Milk and Milk Products**

and keeping intake of fatty and sugary foods low.

GREATER GLASGOW HEALTH BOARD

FRUIT AND VEGETABLES

These are good sources of vitamins A and C and also contain fibre, folic acid, vitamin E and iron.

AIM TO HAVE AT LEAST FIVE SERVINGS PER DAY

Examples

- Fruit juice at breakfast
- Salad or tomato with a sandwich as a snack meal
- Vegetables (fresh, frozen or tinned) with a main meal
- Fresh, stewed or tinned fruit for a dessert
- Fresh fruit as a snack

MEAT, FISH, POULTRY, EGGS, BEANS AND PULSES

These provide protein, iron and B vitamins.

HAVE 2-3 SERVINGS PER DAY AND WITH PLENTY OF VARIETY

Examples

- Day 1 Snack Meal — Tuna in a baked potato or sandwich
  Main Meal — Chicken casserole with rice and vegetables
- Day 2 Snack Meal — Baked beans on toast
  Main meal — Lean meat, vegetables and potatoes

To keep fat low, avoid frying, choose lean meat and make use of pulses and beans which are naturally low in fat.

The oil in fatty fish is beneficial, so try to include sardines, herring, mackerel and tuna regularly.



BREAD, CEREALS, PASTA, RICE, CHAPPATIS AND POTATOES

These provide fibre, B vitamins (including folic acid) and some iron.

PREFERABLY CHOOSE WHOLEGRAIN VARIETIES AND HAVE AT LEAST 5-6 SERVINGS PER DAY

Examples:

- Cereal at breakfast
- Wholemeal roll at breakfast
- Sandwiches as a snack meal
- Potatoes, rice or pasta with main meal
- Toast as supper


MILK, CHEESE AND YOGHURT

These provide protein, calcium and B vitamins.

HAVE 2-3 SERVINGS PER DAY AND CHOOSE LOW FAT VARIETIES. Low fat varieties (with the exception of cottage cheese) contain as much calcium as full fat types.

Examples:

- Semi skimmed milk on cereal and in tea and coffee
- Low fat yoghurt as a dessert
- Low fat cheddar cheese or edam in a sandwich or as a filling for a baked potato

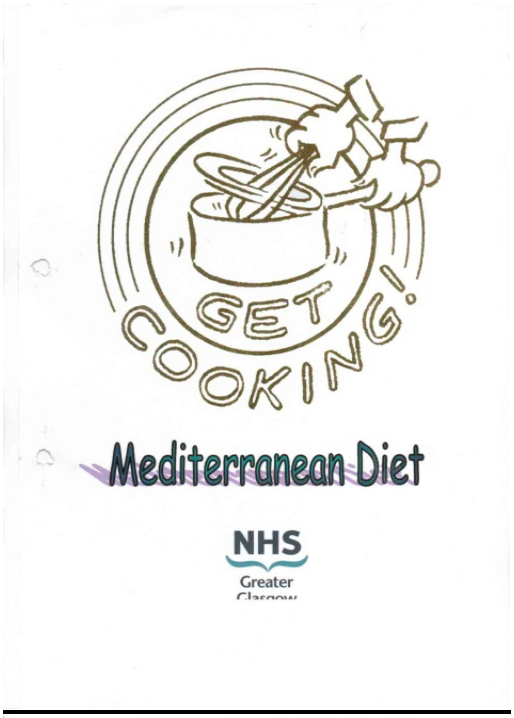

FATTY AND SUGARY FOOD

Eat less often and in small amounts

- Spread butter or margarine thinly on bread
- Grill, bake or microwave rather than fry
- Take tea and coffee without sugar

Cakes, Biscuits, Pastry, Crisps, Chocolate, Sweets and Fizzy Drinks should only be taken as occasional foods


APPENDIX X- SELECTED PAGES FROM PATIENT DIETARY INFORMATION PACK



Get Cooking, Get Shopping is based on a programme run by the Nutrition Team of Greater Glasgow NHS Board. It has been adapted for use in a pilot study of the effect of a Mediterranean Diet intervention with female patients with rheumatoid arthritis run by the Departments of Rheumatology (Glasgow Royal Infirmary, Southern General Hospital and Stobhill Hospital); University Department of Human Nutrition, Glasgow Royal Infirmary; Health Promotion Dept., Greater Glasgow NHS Board.

Topics included in Recipients Pack

- Welcome to 'Get Cooking, Get Shopping'
- Basic Kitchen Equipment
- 'Get Cooking, Get Shopping' 'Get Safe'
- Basic Store Cupboard Ingredients
- Herbs & Spices Know How
- Soups
- Miracles with Mince
- Using Fruit in Cooking
- Fish
- Chicken/Turkey
- Vegetable Main Meals
- Cooking with Convenience
- Cooking for One
- Food Labelling
- Nutritional Labelling
- The Power of Advertising
- Shop & Cook (including planner)
- Recipes

Welcome to Get Cooking

Cooking and shopping are skills everyone needs to be able to look after themselves. Many people see them as something which is passed down and comes 'naturally'. Unfortunately this is not the case and people do not often realise the skills required to successfully cook and shop.

Food is also one of life's greatest pleasures and learning about food can also be a pleasure as well as an essential skill. Good eating habits are vital to maintain a healthy life and it is especially important to establish good eating habits in childhood.

This version of the 'Get cooking, Get Shopping' pack is targeted specifically at people with rheumatoid arthritis. The focus of this pack is cooking and shopping the Mediterranean way. Why are we trying to get people in Scotland to eat more like the Mediterranean people? Well for starters, the Mediterranean Diet is a healthy way of eating but better still medical research suggests that aspects of the Mediterranean diet may actually help improve the symptoms of rheumatoid arthritis.

The aim of this 'Get Cooking, Get Shopping' pack is to put cooking back on everyone's agenda.

The objectives of this pack are:

- Encourage participants to try new foods/ cooking methods
- Encourage participation in group settings
- Learn new skills in relation to reading & understanding labels

There are many myths surrounding cooking and before we start it is important to dispel some of the clouds hanging over home cooking and healthy eating.

Cooking is Difficult
During this course we're going to prove this one wrong, not only that it is not difficult but that it is fun. We'll start of with easy recipes and as your confidence increases we'll move on to slightly more complicated recipes.

Cooking takes a lot of time
All the recipes used in the 'Get Cooking, Get Shopping' course are quick and easy. We try to use as few pots and pans etc. as possible to save on the washing up. Most of the recipes take no more than 30 minutes.

Cooking costs more
Part of the 'Get Cooking, Get Shopping' course includes looking at budgeting and using a wide variety of ingredients. When you think about it, cooking can't be more expensive because, when you buy convenience you will be paying for someone else to make it!

Cooking needs a lot of equipment
All the recipes in this pack require a minimum of equipment, usually things such as a pot, sharp knife, a chopping board and a baking tray. Other equipment can be added as you go along.

You don't know what it's going to turn out like
Unfortunately that's often true of convenience food as well and what's inside the packet is completely different to what is on the packaging.

It doesn't taste the same
That's probably because of all the extra salt, additives, preservatives and flavourings added to convenience foods. Unfortunately for young children this can prove to be dangerous as they can't process too much salt. By making your own food you know exactly what is in it and can make small changes to suit everyone in your family.

Healthy food doesn't taste good
Mediterranean eating is a healthy way of eating and if you've ever been to countries such as Spain or Greece or Italy, then you already know just how good the food tastes. Which dispels the myth that if it's good for you then it can't taste good!

Eating a Mediterranean Diet

The Mediterranean diet is famous for being one of the tastiest and varied cuisines in the world. Due to the way they eat, Mediterranean people also enjoy long and healthier lives than Northern Europeans, with lower incidence of heart attacks, strokes and even cancer.

Following a Mediterranean-style diet does not mean stopping eating what you have always eaten and changing to new, probably more expensive foods. It just means enjoying a wide variety and range of food as possible. So, as odd as it might sound, eating like the Mediterranean's is not as expensive or time-consuming as you might think. The Mediterranean diet is rich in fruit and vegetables, bread, cereals, potatoes and pulses (e.g. dried beans, peas and lentils), incorporates moderate amounts of milk products, fish and poultry and not too much meat or many foods containing fat, sugar and salt.

Eating Mediterranean is all about the proportion of each food group that we eat and enjoying food which is cooked simply, with small amounts of olive oil and plenty of herbs and spices instead of salt. The Mediterranean Diet Pyramid below will give you an easier picture of how much of each food you should be eating to enjoy a Mediterranean diet and a healthier life.

Just remember; No food is bad for you, it depends on how much you eat of it and how often you eat it.

The Balance of Health

Breads, Cereals, Pasta, Rice & Potatoes

In Mediterranean countries breads or cereals are included in every meal and are along with fruit and vegetables are the backbone of the Mediterranean diet.

- These foods are an important source of energy
- They provide fibre, B vitamins and some iron
- Preferably choose wholegrain varieties and have a least 6-11 servings per day


CEREALS, BREAD AND POTATOES

This food group includes:

- Breads, rolls, bagels, pitas, chappatis (made not only from wheat, but also rye, corn and even potato flour!).
- Cereal grains, such as oats, rice and barley.
- Pasta and noodles.
- Potatoes and couscous.
- Starchy vegetables, such as corn.
- Breakfast cereals, muesli and porridge.

Potatoes and starchy vegetables, while not strictly cereals, are often included in this food group as they provide the same kinds of nutrients.

Aim to have at least 6 servings per day

- 1 slice of bread or 1 small roll
- 1 small potato
- 1/2 cup of cooked pasta, rice, or corn
- 30 g (a small bowl) ready-to eat cereals
- 1/2 cup of porridge

See how easy it is to eat 6 or more servings per day

- 1 - 2 slices of toast and a small bowl of cereal at breakfast
- 2 slices of bread as a sandwich at lunch
- 1 cup of rice or pasta with your evening meal

Remember, it's not the bread, pasta or rice that's fattening but what we spread on it or add to it! Try to limit the amount of spread you use on bread and avoid fatty / creamy sauces on your pasta to keep the calories down.

Mediterranean Diet

Fruit


FRUIT AND VEGETABLES

Good source of
- Vitamin A, C & E
- Fibre
- Folic acid

Aim to have at least 3 portions per day
- 1 medium-size piece of fruit (apple, banana, pear, orange, peach)
- 2 small fruits (plums, kiwis)
- 1/2 grapefruit
- 1 slice of large fruit (melon, watermelon, pineapple)
- 1 tablespoon of dried fruit (raisins, apricots)
- 1 handful of grapes, cherries, berries, strawberries
- 2-3 tablespoons of fruit salad or canned fruit
- 1/2 cup fruit juice

- Fruit is an important part of the Mediterranean diet and in most countries it is eaten at the end of the meal, instead of puddings and other desserts.
- Fruit is a quick and easy snack to eat on the run or in between meals.
- Have a glass of fruit juice or some fruit on your cereal at breakfast time.
- During winter when there isn't much variety, use tinned fruit.
- Variety is also important, don't eat the same fruit everyday but try to have at least 3-4 different varieties each week.

Mediterranean Diet

Vegetables

Good sources of
- Vitamin A, C & E
- Fibre
- Folic acid
- Iron

Aim to have at least 3 portions per day

People eating a traditional Mediterranean diet eat about 6 servings of vegetables a day. This is a lot more than what people in Scotland eat. The aim is to try and **eat at least 3 portions a day.** The more the better!

How much is a portion?
- 1/2 cup or 2 tablespoons of cooked vegetables
- 1 cup raw vegetables or salad
- 1/2 cup of vegetable juice

Remember that it is not just the amount that counts but variety is also important. Don't get in a rut and eat the same vegetables day in day out! Try to eat at least 6 or 7 different types of vegetables every week.

Colour is a simple guide to the nutrient content of the vegetable and having a variety of different coloured vegetables not only looks attractive on your plate but will ensure you get the most from the vegetables and salads. Think of vegetables as being red (e.g. peppers and beetroot), white (e.g. cauliflower), green (e.g. spinach and broccoli), blue/purple (e.g. red cabbage) and orange/yellow (e.g. carrots and corn). Eat at least 3 different colours every day.

Don't forget that when fresh vegetables are out of season and expensive that you can use frozen and tinned varieties instead. Frozen vegetables, in particular, are processed close to the time that they are picked and can be higher in nutrients than some of the fresh vegetables that have been lying around in your fridge for a few days.

Mediterranean Diet

Beans and Pulses

Beans and pulses (also called legumes) are eaten regularly in Mediterranean countries and feature in at least 2-3 meals a week.


MEAT, FISH AND ALTERNATIVES

Good sources of
- Protein
- Fibre
- B vitamins
- Iron and calcium

Aim to have at least 2 portions per week

½ cup of cooked beans or lentils equals are serving.

Example
- Baked beans on toast
- 1 cup of lentil soup or split pea soup
- Chickpea curry or lentil stew

Meat, Fish, Poultry, Eggs

- These provide protein, iron & B vitamins
- Fish is rich in polyunsaturated fat, which can protect against heart disease

Aim to have:
- At least 2 servings of fish per week
- No more than 4 servings of poultry per week
- 1 serving of red meat per week
- 3 eggs per week

Whenever possible, choose lean meats and poultry, remove skin and trim visible fat before cooking and limit consumption of fatty meat products, like sausages, salami and other processed meats.

While meat is eaten in Mediterranean countries, it is not eaten every day or in large amounts. It is usually eaten in mixed dishes such as casseroles containing vegetables and dried beans.

Have 1 or 2 meatless main meals every week. Meals based on vegetables and cereals are not only good for you but the also tend to cost less.

Mediterranean Diet

Milk, Cheese & Yoghurt

- These provide protein, calcium & B vitamins
- Have 2-3 servings per day and choose low fat varieties


MILK, CHEESE AND YOGHURT

Example
- Semi skimmed milk (2% fat) on cereal and in tea & coffee
- Low fat yoghurt as dessert
- Low fat cheddar cheese or Edam in a sandwich or baked potato
- Low fat cheese grated over pasta

Mediterranean Diet

Olive oil

A key feature of the Mediterranean diet is the use of olive oil. Olive oil is used in cooking, as well as being drizzled on cooked vegetables and mixed with lemon or vinegar as a salad dressing.

- This oil is rich in monounsaturated fat, which can lower blood cholesterol and protect from heart disease
- It's a rich source of vitamin E, an antioxidant that also protects against heart disease and has been shown in some studies to reduce the symptoms of rheumatoid arthritis.

- Make olive oil your first choice in cooking and replace it for other oils or butter.
- Rather than fry your meats grill them or 'paint' the pan with a little olive oil so the meat won't stick.
- If you use margarine, use a monounsaturated-fat based one, like Bertoli (used to be called Olivio).
- Use olive oil as a salad dressing, instead of mayonnaise or other dressings.
- Steamed vegetables taste delicious with a little olive oil drizzled on top.

Mediterranean Diet

Fatty Foods

- Eat less often and in small amounts

Example
- Try to eat bread without spread. If you use spread, spread only a thin layer
- Cut down on fried foods. Grill, bake or microwave instead
- Avoid eating savoury snacks, like crisps, often. Choose low-fat varieties where available.

Sugary Foods

- Eat less often and in small amounts

Example
- Take tea & coffee without sugar
- Cakes, biscuits, pastry crisps, chocolate, Sweets and fizzy drink should only be taken as occasional foods

Mediterranean Diet

Methods of Cooking

Once you've thought about the type of foods you're going to eat to improve your diet, you need to think about how you're going to cook them. That's what this 'Get Cooking' Programme is all about. Listed below is a summary of some of the methods usually used in Mediterranean cooking. Cooking your meals this way will guarantee you'll make the most out of the foods you buy, like retaining the vitamins and minerals in foods.

- Boiling
- Steaming
- Braising
- Dry Frying
- Stir frying
- Grilling
- Pot roasting
- Microwaving

Mediterranean Diet

Basic Kitchen Equipment

Chopping Boards
Chopping boards are common harbours of bacteria especially if they are wooden. Make sure chopping boards are kept very clean, and if possible have separate boards for raw and cooked foods.

Knives
Sharp knives are the key to cooking however, they are also very dangerous and must be treated with respect. Two knives are all that is really necessary, a good general purpose vegetables knife (Small short flat blade) and a bigger longer bladed knife such as bread knife.
Keep knives stored in a place where children cannot reach and be careful about leaving them lying around the kitchen.

Kitchen Scissors
Keeping a pair of scissors for use only in the kitchen is a good idea. They are often much easier to use for things like cutting up bacon or chicken breast. Ensure they are properly washed between use.

Pots & Pans
A couple of sizes of pots are all you need to get started, a large one for cooking rice, pasta etc. and a smaller one for cooking meat, sauces etc. Try and buy the best you can afford and they will last longer. Check that they are suitable for the kind of cooker you have. A frying pan or a wok is handy as well although not essential.

Wooden Spoons
Every cook needs a wooden spoon! Using wooden rather than metal protects your pot and as long as you ensure you give them a good wash they will last for a reasonable period of time.

Baking Trays/Dishes
These are necessity if you intend cooking in the oven. A couple of large baking trays and an ovenproof dish for things such as Lasagne are ideal.

Measuring Jug/Weighing Scales
A plastic or glass measuring jugs is necessary for measuring liquids and a set of basic measuring scales makes life easier

Although not essential other useful pieces of equipment include:
Grater, sieve/colander, blender, potato peeler, fish slice, tongs, potato masher whisk, tin opener.

'Get Safe'

Following the Mediterranean diet is important but having a **safe Mediterranean diet** is even better. The risk of food poisoning is something we all face everyday whether at home or when eating out.
Every year 4.5 million people suffer from food poisoning - that's 1 in 10 of us! The number of cases of food poisoning have risen over the last few years and we are now all more than ever aware of the importance of safe food handling.

General Hygiene
- Always wash hands before starting cooking and most importantly, after handling raw foods e.g. meat, eggs and vegetables.
- Keep fingernails short and clean.
- Also wash hands after blowing your nose, visiting the toilet, after throwing away waste.
- Do not allow pets in the kitchen, especially on preparation sites, surfaces and equipment.
- Wash down surfaces & equipment with hot water and a detergent, which contains the anti-bacterial agent, after use.
- Cover up any cuts with a waterproof plaster before you start cooking.
- Avoid preparing food for other people if you are suffering from sickness, diarrhoea or a heavy cold.

Shopping Wisely
- Look out for the cleanliness of the store, look at the shelves, floor etc. and also at the staff's own personal hygiene.
- Check 'use by' and 'best before' dates and ensure they are current.
- Foods with a 'use by' date will normally require to be refrigerated to keep them safe. A 'best before' date will indicate how long the food will remain of the expected quality.
- Avoid cans or packaged goods that are damaged.
- Avoid freezer or chiller cabinets which are overfull.
- Avoid dirty or cracked eggs.

Packing it up & Taking it Home
- Separate fresh foods from tinned or dried and wrap meat products and vegetables separately.
- Pack foods that bruise or damage easily above other foods.
- Pack chilled and frozen foods together and take home as soon as possible.
- In warmer weather, pack perishable items in a cool pack or box.
- Do not leave foods, especially fresh food in a car or office, refrigerate immediately.

Storing Food
- Read the labels on packaged food and store as instructed.
- Keep your cupboards, fridge and freezer clean.
- Wipe up any spills immediately.
- Ensure you are rotating your stock and use goods within the appropriate dates. Use older items first - 'first in, first out' principle.
- Ensure your fridge is running at between 1-5°C and your freezer at -18°C.
- Defrost your fridge and freezer regularly to ensure good working order.
- Raw meat must be kept separate from cooked or 'ready-to-eat' foods - keep raw meats on the bottom shelf and keep all foods covered in the fridge.
- Transfer opened packets of dried foods into airtight containers - this prevents moisture or insect contamination.

Care in the Kitchen
- Follow the golden rule- '**clean as you go**'.
- Always wash your hands with soap & water before preparing a meal, after preparing raw meat and vegetables, after visiting the toilet and after touching pets, dirty nappies or the dustbin.
- Clean all work surfaces including knifes and chopping boards before starting to prepare food - remember, we can't see bacteria with our naked eye!
- Avoid cross-contamination at all times - this is the transfer of dangerous bacteria from raw foods to 'ready-to-eat' foods.
- Use separate equipment for raw preparation and cooked/ 'ready-to-eat' - maybe use different colored equipment.
- Minimise using Tea towels for drying equipment - preferably, allow to air dry or use disposal kitchen towels.
- Cloths harbor bacteria - keep clean and use separate cloths on surfaces where raw food has been prepared.
- Wash fruit and vegetables before preparing.
- Keep pets out of kitchen whenever possible.

- Cool and cover leftovers as quickly as possible and then store in the freezer or fridge.
- Do not let flies land on food, keep it covered.
- Empty the bin regularly.

Careful Cooking
- Meat, meat products and poultry need special care as they cause most food poisoning outbreaks.
- Cook meat thoroughly - any juices should run clear when pierced with a knife.
- Defrost raw meats in a separate area of the fridge and in a container to catch any juices.
- All foods must be thoroughly defrosted before cooking, otherwise normal cooking times will only melt the remaining ice in the centre.
- Once thawed never re-freeze unless you cook it first.
- After food is cooked keep in fridge for no longer than 1-2 days.
- If re-heating food, make sure it is piping hot right through, do not reheat more than once.

Basic Store Cupboard Ingredients

This is just a brief outline of some basic store cupboard ingredients you may like to keep on hand to be able to pull together a quick and Mediterranean-style meal. You do not need to go out and buy these all at once, but maybe when you shop each week you could buy one thing extra and over a period of time, it will build up.

Food	Useful For	Where to store and How long
Lentils/ Soup Mix and other dried beans and peas	Useful for soups and also for bulking out mince and stews	In cupboard for 6-12 months
Pasta	Endless options, from a simple boiled dish through to pasta bakes or pasta salad	In cupboard up to 1 year
Rice	For savoury dishes, salad or made into Rice pudding	In cupboard up to 1 year
Noodles	Something different from rice & pasta, good with chicken and vegetable based dishes	In cupboard up to 1 year
Tinned Fruit	Puddings, fruit salad, quick crumbles, pineapple for through sweet & sour dishes. Choose fruit tinned in natural juice instead of syrup.	In cupboard up to 2 years
Tinned Vegetables	Just on their own, with a meal, through pasta, risotto, in soup or stew. Choose low-salt varieties, when available.	In cupboard up to 2 years
Tinned Fish e.g. tuna, salmon, sardines	Tuna and salmon are good trough pasta while sardines on toast make a healthy lunch. Choose varieties tinned in water or brine, instead of oil.	In cupboard up to 2 years
Cereals and porridge oats	For breakfast. Choose wholegrain or high-fibre varieties and watch the salt and sugar content.	In cupboard up to 1 year
Tinned Soup	Watch the salt content but good stand by on its own or if Campbell's Condensed as a sauce for pasta	In cupboard up to 2 years
Pasta or Ready to Serve Sauces	Watch for salt and sugar content but good for a quick meal such as Sweet & Sour Vegetables or tomato based pasta sauces	In cupboard up to 1 year

Stock Cubes (Chicken, ham Beef, Vegetable)	For making a quick pot of soup- beware of the salt content, especially if cooking for young children	In cupboard up to 6 months
Flour (Self Raising /Plain)	All sorts of things including bread, cakes, scones, crumbles & sauces. Experiment with wholegrain flour, when available.	In cupboard for around 6 months
Worcestershire Sauce	In curry, in pasta, anything that needs a 'kick'.	In cupboard up to 1 year
Cheese	In pasta dishes or in baked potatoes. Again watch salt content and choose low-fat types when available.	Up to 4 weeks in the fridge
Cold meat	Serve with potatoes and veg for a quick meal or on sandwiches for packed lunches. Choose low-fat types when available.	Up to 1 week in the fridge

'Herbs & Spices Know How'

A variety of herbs, spices and seasonings are used in Mediterranean cooking in order to enhance the flavour and taste of foods. Again like the store cupboard ingredients, you don't need to go out and buy all these herbs and spices in one go. Gradually build up your collection and you will be amazed at how much of a difference it makes to your cooking. Herbs are especially useful if you are trying to reduce the salt in your diet. Many people use salt to taste cooking whereas they could equally and more tastily use herbs and also reduce their salt intake. Herbs and spices tend to last for quite a long time so ensure the ones you do buy have good fitting lids or caps to ensure their freshness. To save you some money, try and buy with a friend and split them. This will also help you to build up your collection quicker.

Herb/Spice	What to use it in
Mixed Herbs	Minestrone & tomato soups, Italian dishes, omelettes, chicken & vegetable dishes, pasta dishes
Basil	Rice, pasta, soups and tomato based sauces. Also good with mixed vegetable dishes.
Dill	Salads, fish, potatoes, roasted vegetables.
Cumin	Soups, Mexican dishes, curried dishes, chilli dishes, meatballs
Chilli Powder	Rice, pasta, chilli-con-carne, potatoes, meatballs
Oregano	Italian dishes such as lasagne, minestrone soup, roast chicken, tomatoes, courgettes.
Bay leaves	Lentil soup, mince.
Coriander	Carrot, tomato soup, fish, all stews, curries, carrots, celery.
Cinnamon	Biscuits, scones, crumbles, yoghurt, melon, chicken dishes, mince
Ginger	Biscuits, scones, fruit crumbles, chicken stir fries, sweet & sour dishes
Curry	Different strengths for different dishes, good with chicken, beef, pork, vegetables.

Soups

Soups are part of our natural heritage, but over the last few years we've lost some of the skill involved in soup making. More and more tinned soups have become available as well as fresh soups. Although tinned soups are handy they tend to be highly processed with large quantities of salt and sugar.

Home made soup tastes very different from bought and is an ideal way of encouraging children to eat more vegetables. Also because you are making it you know exactly what is in it which is very important for young children. Soups can be introduced to babies from a young age as long as there is no salt added and it is made without stock cubes.

A blender or liquidiser is very useful when making soup as it allows you to make different varieties and puree them which often encourages children to eat them.

Soups are an ideal way of using up vegetables which you've maybe had for a few days, and using combinations of vegetables you wouldn't normally put together.

Here are a few suggestions for you to choose from to make:

- Carrot
- Lentil
- Minestrone

Once you have made your soup, compare it to a tinned or packet version for taste and cost. Remember the cost of your home make soup will be for a bigger volume than the tin or packet. Also have a look at the amount of additives, preservatives and flavouring in the packets/tins.

'Miracles with Mince'

In this section we're going to look at what you can do with mince- whether that is minced beef, lamb, pork or turkey.

Mince is a very versatile product which can be turned into an amazing range of dishes. Using the different types (chicken, turkey, pork) of mince increases the variety again. When buying mince be careful of the quality-some of the cheaper cuts can be up to 20% fat. These will appear cheaper in money terms but once you start cooking it you'll be left with a lot less meat once the fat is melted and then drained away!

Try and buy mince with the lowest fat content - 5 or 6 %, even if it means buying less e.g. 200g instead of 300g. You'll end up just putting the extra 100g down the sink as fat.

Mince can be bulked out in lots of ways to make it go further without affecting the taste. Adding vegetables or lentils are the easiest and quickest way as well as being cheap. Also if you cut vegetables up finely and mix it through mince, children will often never notice and eat it up!

- Beef Chilli with Rice
- Easy Shepherds Pie
- Spicy Meatballs with Penne Pasta

Using Fruit in Cooking

To maintain optimum health we are recommended to eat five portions of fruit and vegetables per day. This is the minimum amount you should eat and people in Mediterranean Countries eat lots more than this. The more the better! To achieve maximum benefit from this we need to eat a good variety of mixed fruit and vegetables.

People in Mediterranean countries usually finish their meal with a piece of fresh fruit or a slice of fresh melon. Puddings and desserts are usually eaten on special occasions and not every day. However, using fruit in puddings is another way of encouraging fruit consumption especially in children.

Some of the ideas for using fruit are very quick and easy whereas others take a bit longer in the oven etc. Things like crumbles are ideal if you have some fruit that is starting to go soft- it doesn't all need to be of the same variety, try variations such as apple and strawberry/raspberry, nectarine and apple, plum and pear etc. and then for a really quick option try using tinned fruit. Using oats in the topping not only adds flavour and crunch but increases the fibre content.

Fruit smoothies are also an ideal way of increasing children's fruit consumption as well as increasing their calcium intake through milk or yoghurt.

Apart from fruit actually in pudding it is a good habit to include fruit with any pudding. So if you are having ice cream have some fruit (fresh or tinned in juice) with it, if your kids are having a yoghurt or fromage frias add some fruit, apple pie add some extra fruit etc.

Why not try some of the following recipes:

- Pear crumble
- Fruit trifle
- Rhubarb Toad in the Hole
- Scones
- Banana Bread
- Tangy Bread & Butter Pudding

Fish

Many myths and ideas surround fish and as a result many people avoid eating or cooking it. People think it goes off easy, you can overcook it and generally are unsure what to do with it. Fish is also often perceived to be expensive, however over the last few years fish has become comparable with beef and chicken and in some cases salmon can be cheaper than mince.

Fish is very important in our diet for a variety of reasons

- Good source of protein
- Good source of calcium
- Oily fish contains fatty acids which can actually help prevent heart disease
- Very low in fat and calories

Nutritional Content of Fish

Per 100g	Haddock	Herring
Protein(g)	19	17.8
Fat(g)	0.6	13.2
Carbohydrate(g)	0	0
Energy (Kcal)	81	190

Choosing & Buying Fish

Where you choose to buy you fish depends on what you are looking for and where you shop. There are not many fishmongers around now, although in some areas fish vans still come round once a week. Your local supermarket or shop may however have some frozen or have a fresh fish counter

What to look for:

- Fish should smell fresh
- Eyes should not be shrunken but clear & bright
- Flesh should be fairly firm to touch
- Whole fish should be moist, shiny skin with bright natural colouring
- Frozen fish should be frozen hard with no signs of thawing

Storing Fish

- Fresh fish should be rinsed, pat dry, cover with cling film and store at the bottom of the fridge.
- Ready to eat fish such as mackerel, prawns etc. should be stored above raw foods in the fridge.
- Frozen fish should be stored at -18°C or less and then thawed out in the fridge.

In this section we want to show that fish is versatile, easy to work with and cost effective. The object of this section is to let you try as many different types of fish as possible, some are more expensive than other, but it is good to be able to take advantage of any special offers etc. if you know how to cook it.

Recipes

To experiment with fish we are going to try some of the following recipes:

- Mackerel & Pasta Supper
- Fisherman's Pie
- Tikka Cod
- Quick Tuna Pasta

Chicken/Turkey

Chicken has become over the last few years the most popular meat consumed in Britain. This is ideal from a health point of view depending on how we cook it. Chicken and turkey are naturally low in fat and high in protein as well as providing a range of minerals. Turkey has become popular other than just at Christmas time, and is often cheaper than chicken with very little taste difference.

Nutritional Content of Turkey and Chicken

Per 100g	Chicken (skinless light meat)	Turkey (skinless light meat)
Protein(g)	24	24.4
Fat(g)	1.1	0.8
Carbohydrate(g)	0	0
Energy(kcal)	106	105

Buying & Storing Chicken /Turkey

Chicken and turkey come in many forms and can be bought frozen or fresh. Frozen chicken is often cheaper but you have to ensure you take it home and re-freeze it immediately or defrost and cook before refreezing. Often buying bigger packs works out cheaper than buying smaller although if you don't have freezer space this is of little value. Sometimes it's worth thinking about going shopping with a friend or relative and sharing packs of meat or chicken.

Chicken legs are ideal for barbecues, grilling or lunch boxes.

Quarter portions are ideal for casseroles or cooked and used in curry or stir fry.

Breast or breast fillets are ideal for curry, stir fry. Risotto etc.

Minced turkey is ideal for lasagne, chilli, shepherds pie etc.

Whole chicken /Turkey are useful for a roast chicken dinner or to use in a curry or soup

Extreme care must be taken when storing chicken & turkey. Chicken in particular is associated with many outbreaks of Salmonella food poisoning every year.

Points to remember:

- Store at the bottom of the fridge
- Defrost thoroughly before use
- Cook thoroughly
- Chill quickly if not eating straight away
- Only re-freeze chicken if cooked in-between.
- Wash hands regularly when handling chicken and before starting to prepare any other foods

In this section we are going to try out a variety of recipes using both chicken and turkey to show how versatile and quick poultry is to cook with.

Recipes:

- Turkey Stir Fry
- Chicken Curry
- Spicy Turkey Risotto
- Quick Chicken Casserole
- Turkey Biriani

Vegetable Main Meals

Whether you are vegetarian or not, vegetable main meals add variety to the diet. They are often lower in fat than meat based dishes as long as you don't start adding lots of additional fats.

Many people perceive vegetables as being accompaniments to meals rather than forming the main part. Many vegetables can be made into a range of exciting dishes similar to meat based as well as forming there own range of unique recipes.

Buying Vegetables

- Get to know your local greengrocer or the person in charge of the fruit and veg in your local supermarket.
- Buy vegetables regularly in small amounts to maintain their vitamin content.
- The lowest cost vegetables are usually cabbages, cauliflower, broccoli, mixed vegetable (frozen) and frozen peas.
- Use tinned and frozen, the nutritional content is as good.
- Buy tinned veg in water with no added salt or sugar.
- Tinned tomatoes are a cheap source of vegetables as well as providing bulk to dishes such as vegetable lasagne or chilli.
- Choose vegetables that are not damaged or bruised.
- Loose veg is usually cheaper than pre-packaged.
- Shop with a friend/relative/ neighbour so you can take advantage of any special offers etc.
- Try and choose a selection of different coloured veg it not only brightens up your plate but also ensures you get a variety of vitamins and minerals.

Storing Vegetables

- Store root vegetables in a cool dark place
- Store salad veg in the fridge along with broccoli, peppers, cauliflower etc.
- Remove packaging from veg to allow to breathe

Preparing & Cooking Vegetables

- Prepare vegetables as close to time of cooking as possible to maintain nutritional content
- If possible leave skins on and wash well as many of the nutrients are found right under the skin
- Try and keep vegetables as chunky as possible as this reduces the surface area for nutrient loss.
- Do not leave vegetables lying in water, the vitamins drain out.
- Try and use quick cooking methods to retain nutrient content.
- Microwaving retains more of the nutrients especially vitamin C as they are cooked in less water.
- Use the water from cooking veg to make gravies or stock for soup.

Vegetable curries or pasta-based dishes are often a good way of encouraging children to eat more vegetables as they can often be made similar to their favourite takeaway.

Try making some of the suggested dishes below and find out just how flexible vegetables can be as well as making a tasty alternative to meat.

- Mushroom & Pepper Stroganoff
- Multi Couloured Stir Fry
- Cheese & Veg Filled Pittas
- Vegetables Balti
- Vegetable Lasagne
- Vegetable Pancake Pizza

Mediterranean Diet

Cooking with Convenience

Convenience products are often seen as being 'bad' for you. In many cases they are often not the most healthy of choices but some are better than others. This course does not advocate eating no convenience foods but learning to use those that are a healthier option.

The key to using convenience food successfully is in reading the labels, convenience foods are notorious for being high in fat, sugar and salt as well as being packed with additives, preservatives and flavourings. These things infrequently are not a big problem but a diet made up solely of convenience products with their associated problems can have a detrimental affect directly and indirectly.

Convenience foods to avoid:

- Ready made frozen meals- expensive and don't tend to have best quality meats and vegetables (if any veg at all)
- Processed meat products (e.g. pies, pastries, chicken nuggetts, burgers) - the meat quantity is often low as well as being of poor quality.
- Tinned soup- tend to be very high in salt, look for ones which are lower or make you own
- Packaged pasta, noodle's etc. such as Pot Noodles are very high in salt

Convenience food you can make work for you

- Tinned & frozen vegetables & fruit, choose fruit in fruit juice and veg in unsalted water
- Pizza bases, - add your own topping, especially vegetables
- Jars of pasta sauces/ready made sauces such as tomato based, sweet & sour etc. Just watch the fat and salt content.

Try some of the following recipes and see how you can make convenience work for you

- Quick Tuna Pasta
- Quick Veg Pizza

Mediterranean Diet

Cooking for One

At various times in our life we can find ourselves only cooking for one, maybe an elderly person, a single parent who's child has just left home or indeed a young person setting up on their own for the first time. Whatever the circumstance it's quite a daunting prospect.

For some it may be about learning to cook and shop full stop while for others it may be about changing the way and amount you cook. The main advantage of shopping and cooking for one is you can buy and cook what you like, you don't have to consider anyone else's likes and dislikes! What ever the circumstances here are some tips and ideas to get you used to the idea of shopping and cooking for one.

Shopping

- Use the store to your advantage. Just because you are buying fruit and veg for one does not mean you cannot have variety. Buy things loose if you only want one pear, or one parsnip only buy one!
- Use the delicatessen to your advantage. If you only want a little pot of potato salad to go with your lunch buy it loose rather than buying a larger pot from the chillier cabinet.
- The deli is also useful for cold meat- if you don't want to cook a piece of roast beef or roast pork, buy the number of slices you want and make the gravy when you get home.
- The deli again is useful for things like sausages or bacon. Making a pasta dish and want a couple of slices of bacon- well just buy a couple.
- Again if your supermarket has a butchers or fishmonger, feel free to buy the amount you need and want.
- Tinned fruit, vegetables and fish are good standby ingredients- try and keep a few small tins of these in your cupboard.
- Pasta and Rice tend to come in a variety of sizes, buy as big a one as you have room to store and you can afford. They both keep for a long time and are useful when you are cooking for one.
- Buy a packet of chicken breasts and divide them up and freeze them or buy loose from the butchers.

Mediterranean Diet

Cooking

- Many recipes and dishes you normally make can be adapted for one
- Soups are useful. Don't make huge pots make enough for today, tomorrow and a dish for the freezer. If you have freezer space, getting a few freezer proof dishes is very useful not only for soup, but mince/chicken dishes.
- Mince dishes are handy. Either just buy your mince loose enough for one portion or buy a bigger pack and make a basic savoury mince recipe. Have it today with spaghetti and tomorrow into an individual dish of Lasagne. Again if you have freezer space, freeze a portion for chilli another day.
- Stir Fry's are ideal for one as you can cook a chicken breast with lots of vegetables add some sauce and serve with rice, pasta or noodles.
- Risottos are also ideal as you can just make enough or how about making double and taking some for lunch next day.
- Pasta dishes can also be make just for one, make sure you add lots of vegetables.

The secret of cooking for one and enjoying it is to try and have as much variety in your diet as possible. Many people get the idea that when there is only one person its not worth going to any hassle. You need to turn this round and make cooking for yourself an enjoyable experience and that you are worth making an effort over what ever the circumstances.

Try some of these recipes

- Fish Finger Pie
- Vegetable Risotto

Mediterranean Diet

Food Labelling

Food labels are intended to give you information to help you choose appropriate foods for you and your family. However in many cases, labelling is used as advertising, and can become very confusing for the consumer.

Within this session of 'Get Cooking, Get Shopping' we want to try and iron out some of these issues and try and make things a bit clearer.

By law each label must contain the following:

- The name of the food
- List of ingredients
- Durability Indication
- Name & Address of either manufacturer or seller
- Particulars of place of origin
- Weight

The Name of the Food

This is required to let the customer know what the product actually is. If the name does not fully describe it, a full description must be provided.

List of Ingredients

These include foods, additives and added water (over 5%). They are listed with the greatest first. For additives it will give names or E numbers and say whether it is a preservative, colouring or flavouring. Although this tells you what's in a product, it gives you no indication of the quantities used. Look at the example of a cereal label below:

Ingredients:
Wheat bran, sugar, salt, malt, niacin, honey, vitamin B_6, riboflavin(B_2), thiamine (B_1), vitamin D_3

Durability Indications
This will indicate how long the product can be stored. This will usually be either worded as 'Best Before', 'Best Before End' or 'Use By' followed by the date specified. This area of the label will also contain an indication of how the product should be stored ('Keep in fridge 2 to 5°C' or 'Store in a cool dry place'). 'Use by' applies to products that will become inedible within a few days and after this date present a risk to health (e.g. Fresh meat). 'Best Before' and 'Best Before End' apply to products that are best eaten before the date given. However, if eaten after this date there would be no risk to health, although the product quality may have decreased.

Name & Address of Manufacturer or Seller
This will indicate who is responsible for the product, usually located on the back of the product and will indicate where the consumer should send any queries or questions.

Particulars of place of Origin
This will indicate where the product has been produced. This is only required where the consumer can be misled. The Co-op ensure this is on all their products.

Weight
Most products are required to display the weight although some are exempt, such as meat pies and sausages.

Nutrition Labelling

By law, labels do not have to give nutrition information, UNLESS they make a nutritional claim for the product such as LOW FAT. However, many labels do give nutrition information anyway, but where they do, they must by law, do it in one of two ways:

Big 4: Energy (kJ & kcal), protein, carbohydrate & fat
Big 4 & Small 4: Energy (kJ & kcal), protein, carbohydrate, sugars, fat, saturated fat, fibre and sodium.
In addition they can give vitamins and minerals when present in significant amounts.

This means that manufacturers cannot decide to give only the nutrition information that suits their product. E.g. if a product is high in fat they cannot just give values for energy, protein and carbohydrate, and exclude fat.

Nutrition Information per 100g	
Energy	351 kJ/ 83 kcal
Protein	2.7g
Carbohydrate	16.4g
Fat	0.7g

Nutrition Information per 100g	
Energy	351 kJ/ 83 kcal
Protein	2.7g
Carbohydrate	16.4g
Of which Sugars	0.4g
Fat	0.7g
Of which Saturates	0.2g
Fibre	1.0g
Sodium	0.2g

Nutrition-per 100g or per item??

When providing nutrition information, by law nutrition values per 100g of the food have to be given. Values per serving can only be given in addition to the per 100g information, not instead of.

Per 100g information is useful if you are comparing two or more products. e.g. Cheddar cheese and Edam cheese. You can look at the per 100g to see which you prefer.

NUTRITION - EDAM	
TYPICAL VALUES	PER 100 g
Energy Value	1370 kJ
(Calories	330 kcal)
Protein	26 g
Carbohydrate	Trace g
(of which Sugars)	Trace g)
Fat	25 g
(of which Saturates	16 g)
Fibre	Nil g
Sodium	1.0 g

NUTRITION - CHEDDAR	
TYPICAL VALUES	PER 100 g
Energy Value	1750 kJ
(Calories	410 kcal)
Protein	25 g
Carbohydrate	0.1 g
(of which Sugars)	0.1 g)
Fat	34 g
(of which Saturates	22 g)
Fibre	Nil g
Sodium	0.3 g

Eg. The cheddar has more fat, but has less sodium than the edam

Per serving / item is useful if you are trying to count calories or control your fat intake as it tells you the amount you will actually eat in a serving. It is also useful if you are deciding between products of different sizes. Eg. Strawberry Mousse 62g or Raspberry Trifle 125g

NUTRITION - MOUSSE		
TYPICAL VALUES	PER POT (62g)	PER 100 g
Energy Value	530 kJ	860 kJ
(Calories	130 kcal	205 kcal)
Protein	2 g	3 g
Carbohydrate	10 g	17 g
(of which Sugars	10 g	16 g)
Fat	9 g	14 g
(of which Saturates	5 g	9 g)
Fibre	Trace g	Trace g
Sodium	Trace g	0.1 g

NUTRITION- TRIFLE		
TYPICAL VALUES	PER POT (125g)	PER 100 g
Energy Value	870 kJ	700 kJ
(Calories	210 kcal	165 kca
Protein	3 g	2 g
Carbohydrate	27 g	22 g
(of which Sugars	24 g	19 g)
Fat	10 g	8 g
(of which Saturates	6 g	5 g)
Fibre	0.4 g	0.3 g
Sodium	Trace g	Trace g

Although the mousse has more fat per 100g, if you eat either all the mousse or all the trifle, there is more fat in the serving of trifle than there is in the serving of mousse.

GUIDELINE DAILY AMOUNTS
Each person has different food needs. Some food labels give you a quick guide:

GUIDELINE DAILY AMOUNTS			Per Pizza
	Women	Men	
Calories	2000	2500	710
Fat	70g	95g	23g
Salt	5g	7g	4.3g

These figures are for average adults of normal weight. Your own requirements will vary with age, size and activity level.

If you are eating 2000 Calories in a day, then 70 grams of fat and 5 grams of salt are guidelines for levels of fat and salt you should aim to stay below. The example above shows that if you eat the whole pizza it will give you approximately 1/3 of your 2000 calories, approximately 1/3 of your fat, but nearly all your salt. You need to watch your salt intake from your remaining foods that day.

Recommended Daily Amounts (RDAs) for Vitamins and Minerals
Extra information is given on products such as breakfast cereals which contain added vitamins and minerals' because it helps us to judge what's a lot and what's a little. It does this by giving us the amount of the vitamin / mineral as a percentage of the recommended daily amount (RDA).

NUTRITION		
TYPICAL VALUES	PER 40 g SERVING	PER 100 g
Energy Value	640 kJ	1610 kJ
(Calories	150 kcal	380 kcal)
Protein	2 g	5 g
Carbohydrate	33 g	82 g
(of which Sugars	13 g	32 g)
Fat	1 g	3 g
(of which Saturates	0.2 g	0.6 g)
Fibre	1 g	3 g
Sodium	0.2 g	0.5 g
Vitamin D	2.0 ug	5.0 ug
(% of the R.D.A.	40 %	100 %)
Thiamin (B1)	0.6 mg	1.4 mg
(% of the R.D.A.	40 %	100 %)
Riboflavin (B2)	0.6 mg	1.6 mg
(% of the R.D.A.	40 %	100 %)
Niacin	7.2 mg	18 mg
(% of the R.D.A.	40 %	100 %)
Iron	3.1 mg	7.8 mg
(% of the R.D.A.	22 %	56 %)

If we eat a 40gram serving of this cereal, we will get 40% (nearly 1/2) of our daily requirement for vitamin D, B_1, B_2 and Niacin, and 22% (nearly ½) of our requirement for iron.

Salt
As a rough guide salt = 2.5 x sodium

APPENDIX XI – MEDITERRANEAN-TYPE DIET RESULTS POSTER

WHAT IS A MEDITERRANEAN-TYPE DIET?

This is a diet common to areas around the Mediterranean Sea: including parts of Spain, France, Italy and Greece. It is typically **rich in olive oil, fish, fruit and vegetables and low in saturated fats**. It has been associated with health benefits for the heart, blood vessels and joints.

OUR STUDY

We designed this study to try to overcome obstacles to healthy eating in some areas of Glasgow.

130 females with rheumatoid arthritis who attended rheumatology clinics at Glasgow Royal, Stobhill or Southern General Hospitals volunteered for this study. 55 were given written information only on diet, while the other 75 attended cookery classes for 6 weeks on the Mediterranean-type diet. Everyone had their arthritis and blood pressure monitored, as well as completing food diaries.

RESULTS OF OUR STUDY

The diet group **ate significantly more fruit and vegetables** and **lost more weight** than the other group. Their **blood pressure fell**: the systolic blood pressure (the top number) fell from an average of 132 to 128. While this may not look that impressive on paper, even a small drop in blood pressure can have beneficial effects on your heart and blood vessels

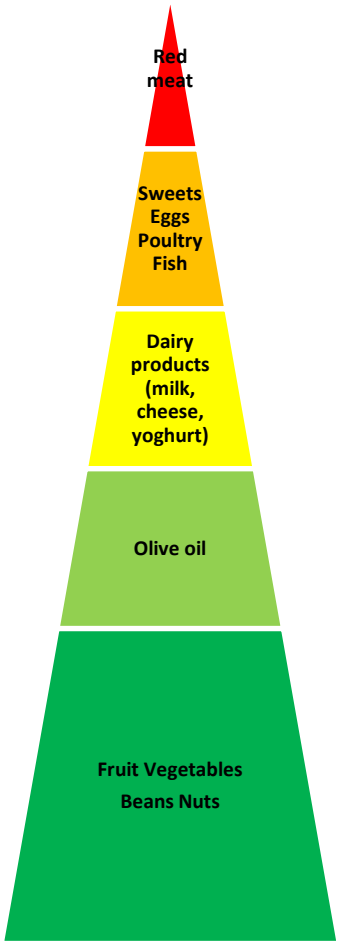
With regards to arthritis, the diet group felt their **joints were less painful, stiff and swollen** and that they were **less stiff in the morning.**

IMPORTANCE OF THIS STUDY

We think that this is an important study and are encouraging all of our patients to look at how they could make improvements to their diet to help their arthritis and potentially their blood pressure. Diet will never cure arthritis nor replace all of your drug treatments, but it can make a big difference to how you are feeling.

PYRAMID OF FOOD INTAKE

You should take less of the items at the top of the pyramid and more from the bottom.



Adapted from: WC Willett et al, "Mediterranean diet pyramid: a cultural model for healthy eating". American Journal of Clinical Nutrition 1995 61(6 Suppl):1402S-1406S

APPENDIX XII – JOINT BRITISH SOCIETIES CORONARY RISK PREDICTION CHART

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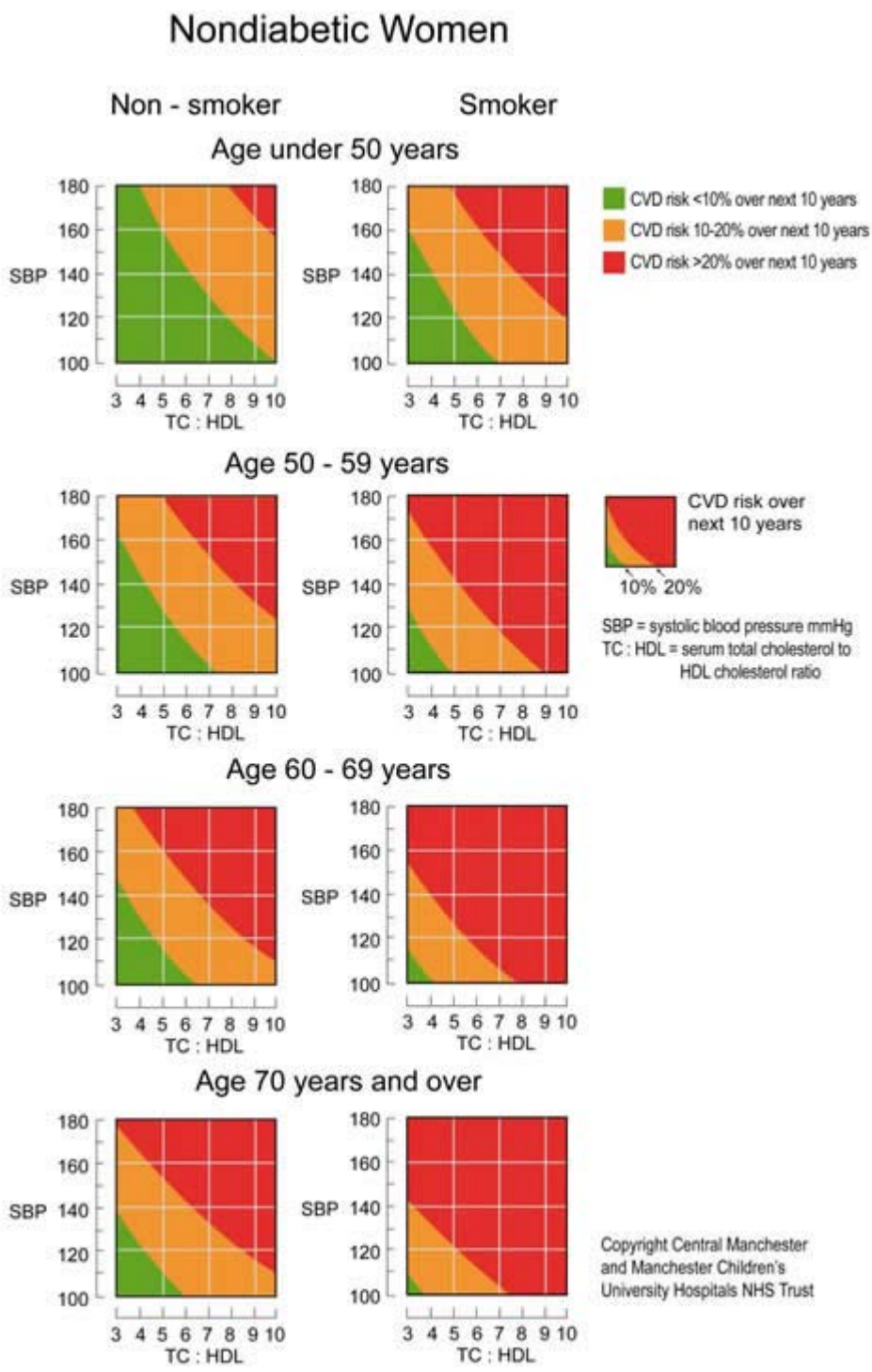
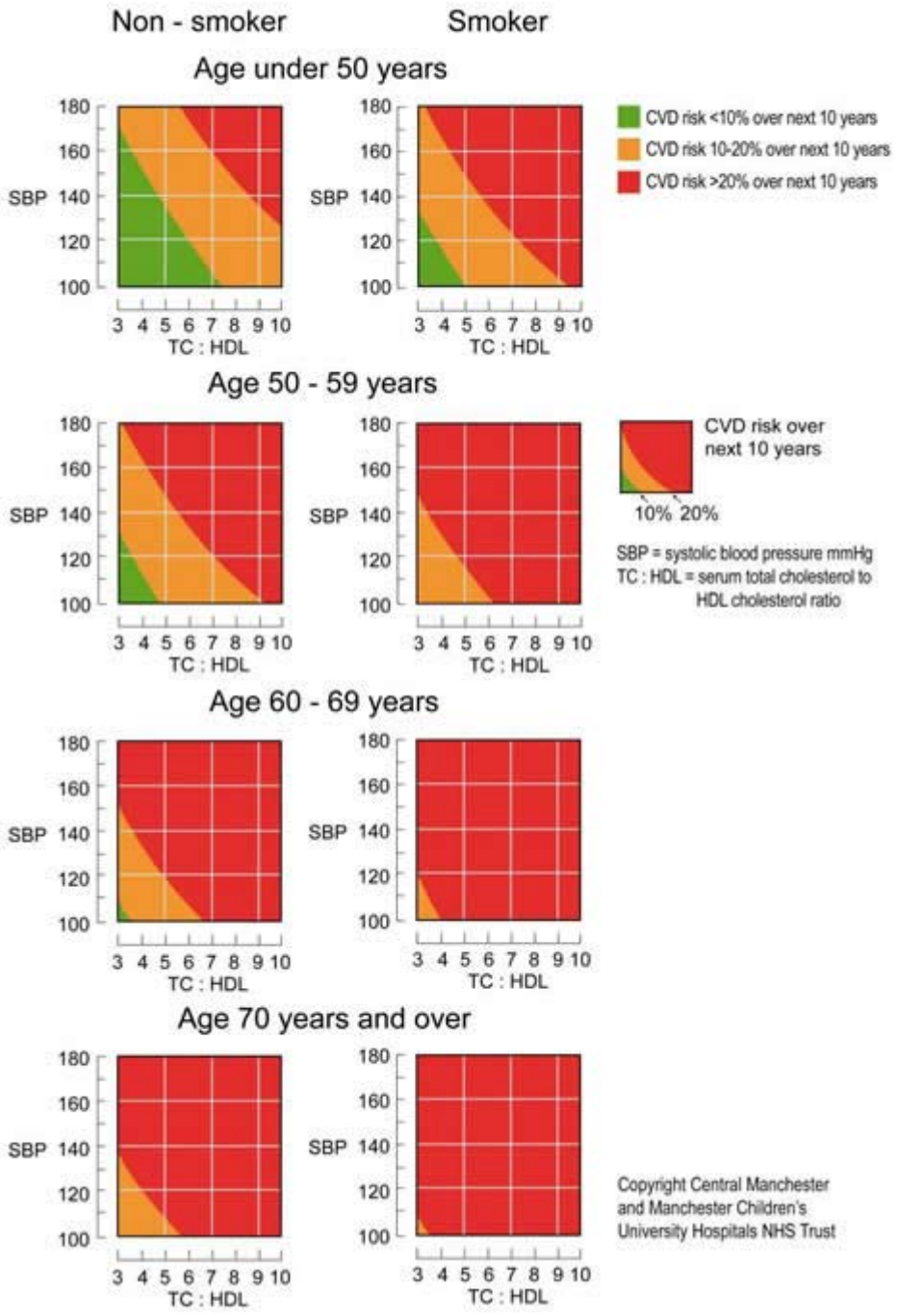


Nondiabetic Men



REFERENCES

1. Garrod A. Treatise on nature and treatment of gout and rheumatic gout. London: Walton and Maberly; 1859.

2. Storey GD. Alfred Baring Garrod (1819-1907). Rheumatology. 2001; 40(10):1189-90.

3. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Research & Therapy. 2009; 11(3):229.

4. Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology. 2002; 41(7):793-800.

5. Zeng X, Ai M, Tian X, Gan X, Shi Y, Song Q, et al. Diagnostic value of anti-cyclic citrullinated Peptide antibody in patients with rheumatoid arthritis. Journal of Rheumatology. 2003; 30(7):1451-5.

6. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis & Rheumatism. 1988; 31(3):315-24.

7. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & Rheumatism.2010; 62(9):2569-81.

8. Britsemmer K, Ursum J, Gerritsen M, van Tuyl L, van Schaardenburg D. Validation of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: slight improvement over the 1987 ACR criteria. Annals of the Rheumatic Diseases. 2011; 70(8):1468-70.

9. Alves C, Luime JJ, van Zeben D, Huisman A-M, Weel AEAM, Barendregt PJ, et al. Diagnostic performance of the ACR/EULAR 2010 criteria for rheumatoid arthritis and two diagnostic algorithms in an early arthritis clinic (REACH). Annals of the Rheumatic Diseases. 2011; 70(9):1645-7.

10. Da Silva JAP, Jacobs JWG, Kirwan JR, Boers M, Saag KG, Ines LBS, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Annals of the Rheumatic Diseases. 2006; 65(3):285-93.

11. Kirwan JR, Bijlsma JWJ, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis: Cochrane Database of Systematic Reviews. (1) , 2007. Article Number: CD006356.

12. O'Dell JR, Leff R, Paulsen G, Haire C, Mallek J, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Arthritis & Rheumatism. 2002 May; 46(5):1164-70.

13. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet. 2004; 364(9430):263-9.

14. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (TA130). 2007; Available from: www.guidance.nice.org.uk/TA130

15. NICE. Rheumatoid arthritis - drugs for treatment after failure of a TNF inhibitor (TA195). 2010; Available from: www.guidance.nice.org.uk/TA195

16. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis & Rheumatism. 1995; 38(6):727-35.

17. van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis & Rheumatism. 1998; 41(10):1845-50.

18. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis & Rheumatism. 1981; 24(10):1308-15.

19. Prevoo ML, van Gestel AM, van T Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol. 1996; 35(11):1101-5.

20. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis & Rheumatism. 1995; 38(1):44-8.

21. van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. Journal of Rheumatology. 1993; 20(3):579-81.

22. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LHD, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis & Rheumatism. 2011; 63(3):573-86.

23. Majka DS, Deane KD, Parrish LA, Lazar AA, Baron AE, Walker CW, et al. Duration of preclinical rheumatoid arthritis-related autoantibody positivity increases in subjects with older age at time of disease diagnosis. Annals of the Rheumatic Diseases. 2008; 67(6):801-7.

24. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nature Reviews Immunology 2007; 7(6):429-42.

25. Sattar N, McInnes IB. Vascular comorbidity in rheumatoid arthritis: potential mechanisms and solutions. Current Opinion in Rheumatology 2005; 17(3):286-92.

26. Van Boxel JA, Paget SA. Predominantly T-cell infiltrate in rheumatoid synovial membranes. New England Journal of Medicine. 1975; 293(11):517-20.

27. Edwards JCW, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. New England Journal of Medicine. 2004;350(25):2572-81.

28. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis & Rheumatism. 2006; 54(5):1390-400.

29. Thomson W, Harrison B, Ollier B, Wiles N, Payton T, Barrett J, et al. Quantifying the exact role of HLA-DRB1 alleles in susceptibility to inflammatory polyarthritis: results from a large, population-based study. Arthritis & Rheumatism. 1999;42(4):757-62.

30. Hinks A, Barton A, John S, Bruce I, Hawkins C, Griffiths CEM, et al. Association between the PTPN22 gene and rheumatoid arthritis and juvenile idiopathic arthritis in a UK population: further support that PTPN22 is an autoimmunity gene. Arthritis & Rheumatism. 2005; 52(6):1694-9.

31. McAllister K, Eyre S, Orozco G. Genetics of rheumatoid arthritis: GWAS and beyond: Open Access Rheumatology: Research and Reviews. 2011; 3 (Article 5):31-46.

32. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis & Rheumatism. 1987; 30(11):1205-13.

33. Stahl EA, Wegmann D, Trynka G, Gutierrez-Achury J, Do R, Voight BF, et al. Bayesian inference analyses of the polygenic architecture of rheumatoid arthritis: Nature Genetics 2012; 44(5):483-489.

34. Daha NA, Lie BA, Trouw LA, Stoeken G, Schonkeren JJM, Ding B, et al. Novel genetic association of the VTCN1 region with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2012;71(4):567-71.

35. Raychaudhuri S, Remmers EF, Lee AT, Hackett R, Guiducci C, Burtt NP, et al. Common variants at CD40 and other loci confer risk of rheumatoid arthritis. Nature Genetics. 2008; 40(10):1216-23.

36. Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP, et al. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci: Nature Genetics. 2010; 42(6):508-514.

37. Plenge RM, Seielstad M, Padyukov L, Lee AT, Remmers EF, Ding B, et al. TRAF1-C5 as a risk locus for rheumatoid arthritis--a genomewide study. New England Journal of Medicine. 2007;357(12):1199-209.

38. Feldmann M, Brennan FM, Maini RN. Rheumatoid arthritis. Cell. 1996; 85 (3):307-10.

39. Brennan FM, Chantry D, Jackson A, Maini R, Feldmann M. Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. Lancet. 1989; 2(8657):244-7.

40. Keffer J, Probert L, Cazlaris H, Georgopoulos S, Kaslaris E, Kioussis Kollias DG. Transgenic mice expressing human tumour necrosis factor: A predictive genetic model of arthritis. EMBO Journal. 1991; 10(13):4025-31.

41. Williams RO, Feldmann M, Maini RN. Anti-tumor necrosis factor ameliorates joint disease in murine collagen-induced arthritis. Proceedings of the National Academy of Sciences of the United States of America. 1992; 89(20):9784-8.

42. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999; 354(9194):1932-9.

43. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annual Review of Immunology 1996; 14:397-440.

44. Zhang H, Park Y, Wu J, Chen Xp, Lee S, Yang J, et al. Role of TNF-alpha in vascular dysfunction. Clinical Science. 2009;116(3):219-30.

45. Grisar J, Aletaha D, Steiner CW, Kapral T, Steiner S, Saemann M, et al. Endothelial progenitor cells in active rheumatoid arthritis: effects of tumour necrosis factor and glucocorticoid therapy. Annals of the Rheumatic Diseases. 2007;66(10):1284-8.

46. Quinn K, Henriques M, Parker T, Slutsky AS, Zhang H. Human neutrophil peptides: A novel potential mediator of inflammatory cardiovascular diseases. American Journal of Physiology - Heart and Circulatory Physiology. 2008; 295 (5):H1817-H24.

47. Zhao S-P, Dong S-Z. Effect of tumor necrosis factor alpha on cholesterol efflux in adipocytes. Clinica Chimica Acta. 2008; 389(1-2):67-71.

48. Langman MJ, Jensen DM, Watson DJ, Harper SE, Zhao PL, Quan H, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. Journal of the American Medical Association 1999; 282(20):1929-33.

49. McKellar GE, McCarey DW, Sattar N, McInnes IB. Role for TNF in atherosclerosis? Lessons from autoimmune disease. Nature Reviews Cardiology. 2009; 6(6):410-7.

50. Feldmann M, Maini RN. Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? Annual Review of Immunology. 2001; 19:163-96.

51. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. New England Journal of Medicine. 2000; 343(22):1586-93.
[Erratum appears in New England Journal of Medicine 2001; 344(3):240].
[Erratum appears in New England Journal of Medicine 2001; 344(1):76].

52. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis & Rheumatism. 2003; 48(1):35-45.
[Erratum appears in Arthritis Rheum. 2003 Mar;48(3):855].

53. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. Lancet. 2007; 370(9602):1861-74.

54. Ding T, Ledingham J, Luqmani R, Westlake S, Hyrich K, Lunt M, et al. BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. Rheumatology. 2010; 49(11):2217-9.

55. Wolfe F, Michaud K. The risk of myocardial infarction and pharmacologic and nonpharmacologic myocardial infarction predictors in rheumatoid arthritis: a cohort and nested case-control analysis. Arthritis & Rheumatism. 2008; 58(9):2612-21.

56. Raterman HG, van Halm VP, Voskuyl AE, Simsek S, Dijkmans BAC, Nurmohamed MT. Rheumatoid arthritis is associated with a high prevalence of hypothyroidism that amplifies its cardiovascular risk. Annals of the Rheumatic Diseases. 2008; 67(2):229-32.

57. Raterman HG, van Eijk IC, Voskuyl AE, Peters MJL, Dijkmans BAC, van Halm VP, et al. The metabolic syndrome is amplified in hypothyroid rheumatoid arthritis patients: a cross-sectional study. Annals of the Rheumatic Diseases. 2010;69(1):39-42.

58. Gonzalez A, Kremers HM, Crowson CS, Gabriel S. Survival trends and risk factors for mortality in rheumatoid arthritis. International Journal of Advances in Rheumatology. 2005; 3(2):38-46.

59. Gabriel SE. Why do people with rheumatoid arthritis still die prematurely? Annals of the Rheumatic Diseases. 2008;67 (SUPPL. 3):iii30-iii4.

60. Peters MJL, van Halm VP, Voskuyl AE, Smulders YM, Boers M, Lems WF, et al. Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. Arthritis & Rheumatism. 2009; 61(11):1571-9.

61. Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Torp-Pedersen C, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. Annals of the Rheumatic Diseases. 2011; 70(6):929-34.

62. Turesson C, McClelland RL, Christianson TJ, Matteson EL. Severe extra-articular disease manifestations are associated with an increased risk of first ever cardiovascular events in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2007; 66(1):70-5.

63. van Halm VP, Peters MJL, Voskuyl AE, Boers M, Lems WF, Visser M, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. Annals of the Rheumatic Diseases. 2009; 68(9):1395-400.

64. British Heart Foundation. Coronary Heart Disease Statistics. Available from: www.heartstats.org

65. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation. 1994; 90(1):583-612.

66. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364(9438):937-52.

67. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? Arthritis & Rheumatism. 2002; 46(4):862-73.

68. Van Doornum S, Brand C, King B, Sundararajan V. Increased case fatality rates following a first acute cardiovascular event in patients with rheumatoid arthritis. Arthritis & Rheumatism. 2006; 54(7):2061-8.

69. Van Doornum S, Brand C, Sundararajan V, Ajani AE, Wicks IP. Rheumatoid arthritis patients receive less frequent acute reperfusion and secondary prevention therapy after myocardial infarction compared with the general population. Arthritis Research & Therapy. 2010; 12(5):R183.

70. Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, et al. Increased coronary-artery atherosclerosis in rheumatoid arthritis: Relationship to disease duration and cardiovascular risk factors. Arthritis and Rheumatism. 2005; 52(10):3045-3053

71. Meune C, Touze E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology. 2009; 48(10):1309-13.

72. Kremers HM, Crowson CS, Therneau TM, Roger VL, Gabriel SE. High ten-year risk of cardiovascular disease in newly diagnosed rheumatoid arthritis patients: a population-based cohort study. Arthritis & Rheumatism. 2008; 58(8):2268-74.

73. Kremers HM, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. Arthritis & Rheumatism. 2004; 50(11):3450-7.

74. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis & Rheumatism. 2005; 52(3):722-32.

75. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis & Rheumatism. 2005; 52(2):402-11.

76. Criteria Committee of the New York Association. Nomenclature and criteria for the diagnosis of diseases of the heart and great vessels. Boston, Mass: Little, Brown and Co.; 1994.

77. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis & Rheumatism. 2005; 52(2):412-20.

78. Davis JM, 3rd, Roger VL, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. The presentation and outcome of heart failure in patients with rheumatoid arthritis differs from that in the general population. Arthritis & Rheumatism. 2008; 58(9):2603-11.

79. Bhatia GS, Sosin MD, Patel JV, Grindulis KA, Khattak FH, Hughes EA, et al. Left ventricular systolic dysfunction in rheumatoid disease: an unrecognized burden? Journal of the American College of Cardiology. 2006; 47(6):1169-74.

80. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Jacobsen SJ, Roger VL, et al. Raised erythrocyte sedimentation rate signals heart failure in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2007; 66(1):76-80.

81. Clerico A, Emdin M. Diagnostic accuracy and prognostic relevance of the measurement of cardiac natriuretic peptides: a review. Clinical Chemistry. 2004; 50(1):33-50.

82. Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. New England Journal of Medicine. 2005; 352(7):666-75.

83. Peters MJL, Welsh P, McInnes IB, Wolbink G, Dijkmans BAC, Sattar N, et al. Tumour necrosis factor {alpha} blockade reduces circulating N-terminal pro-brain natriuretic peptide levels in patients with active rheumatoid arthritis: results from a prospective cohort study. Annals of the Rheumatic Diseases. 2010; 69(7):1281-5.

84. Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. Circulation Research. 2002; 91(11):988-98.

85. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. New England Journal of Medicine. 1990; 323(4):236-41.

86. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT, Anti TNFTACHFI. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation. 2003; 107(25):3133-40.

87. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation. 2004; 109(13):1594-602.

88. Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Annals of Internal Medicine. 2003; 138(10):807-11.

89. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360(9349):1903-13.
[Erratum appears in Lancet. 2003;361(9362):1060].

90. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005; 365(9455):217-23.

91. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, et al. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. Journal of Human Hypertension. 2004; 18(3):139-85.

92. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B, Guideline Development G. Management of hypertension: summary of NICE guidance. British Medical Journal. 2011; 343:d4891.

93. Chen YF, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: A systematic review and economic evaluation. Health Technology Assessment. 2008; 12(11):iii-158.

94. Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. Journal of the American Medical Association. 1997; 277(9):739-45.

95. Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet. 2000; 355(9207):865-72. [erratum appears in Lancet 2001;357(9257):724]

96. Neal B, MacMahon S, Chapman N, Blood Pressure Lowering Treatment Trialists C. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet. 2000; 356(9246):1955-64.

97. Glynn RJ, L'Italien GJ, Sesso HD, Jackson EA, Buring JE. Development of predictive models for long-term cardiovascular risk associated with systolic and diastolic blood pressure. Hypertension. 2002; 39(1):105-10.

98. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998; 351(9118):1755-62.

99. Panoulas VF, Metsios GS, Pace AV, John H, Treharne GJ, Banks MJ, et al. Hypertension in rheumatoid arthritis. Rheumatology. 2008; 47(9):1286-98.

100. Panoulas VF, Douglas KM, Milionis HJ, Stavropoulos-Kalinglou A, Nightingale P, Kita MD, et al. Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. Rheumatology. 2007; 46(9):1477-82.

101. Panoulas VF, Douglas KM, Stavropoulos-Kalinoglou A, Metsios GS, Nightingale P, Kita MD, et al. Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. Rheumatology. 2008; 47(1):72-5.

102. Panoulas VF, Toms TE, Metsios GS, Stavropoulos-Kalinoglou A, Kosovitsas A, Milionis HJ, et al. Target organ damage in patients with rheumatoid arthritis: the role of blood pressure and heart rate. Atherosclerosis. 2010; 209(1):255-60.

103. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis & Rheumatism. 2005; 52(11):3381-90.

104. Klarenbeek NB, van der Kooij SM, Huizinga TJW, Goekoop-Ruiterman YPM, Hulsmans HMJ, van Krugten MV, et al. Blood pressure changes in patients with recent-onset rheumatoid arthritis treated with four different treatment strategies: a post hoc analysis from the BeSt trial. Annals of the Rheumatic Diseases. 2010; 69(7):1342-5.

105. Ruiz-Ortega M, Lorenzo O, Suzuki Y, Ruperez M, Egido J. Proinflammatory actions of angiotensins. Current Opinion in Nephrology & Hypertension. 2001; 10(3):321-9.

106. Perry ME, Chee MM, Ferrell WR, Lockhart JC, Sturrock RD. Angiotensin receptor blockers reduce erythrocyte sedimentation rate levels in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2008; 67(11):1646-7.

107. Nelson DL., Cox MM. Lehninger Principles of Biochemistry. 5th ed: W.H. Freeman; 2008.

108. British Cardiac Society, British Hypertension Society, Diabetes UK, Heart UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart. 2005;91 Suppl 5:v1-52.

109. Semb AG, Kvien TK, Aastveit AH, Jungner I, Pedersen TR, Walldius G, et al. Lipids, myocardial infarction and ischaemic stroke in patients with rheumatoid arthritis in the Apolipoprotein-related Mortality RISk (AMORIS) Study. Annals of the Rheumatic Diseases. 2010; 69(11):1996-2001.

110. Toms TE, Panoulas VF, Douglas KMJ, Griffiths H, Sattar N, Smith JP, et al. Statin use in rheumatoid arthritis in relation to actual cardiovascular risk: evidence for substantial undertreatment of lipid-associated cardiovascular risk? Annals of the Rheumatic Diseases. 2010; 69(4):683-8.

111. van Halm VP, Nielen MMJ, Nurmohamed MT, van Schaardenburg D, Reesink HW, Voskuyl AE, et al. Lipids and inflammation: serial measurements of the lipid profile of blood donors who later developed rheumatoid arthritis. Annals of the Rheumatic Diseases. 2007; 66(2):184-8.

112. Kitas GD, Gabriel SE. Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. Annals of the Rheumatic Diseases. 2011; 70(1):8-14.

113. Dursunoglu D, Evrengul H, Polat B, Tanriverdi H, Cobankara V, Kaftan A, et al. Lp(a) lipoprotein and lipids in patients with rheumatoid arthritis: Serum levels and relationship to inflammation. Rheumatology International. 2005; 25 (4):241-5.

114. Munro R, Morrison E, McDonald AG, Hunter JA, Madhok R, Capell HA. Effect of disease modifying agents on the lipid profiles of patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 1997; 56(6):374-7.

115. Allanore Y, Kahan A, Sellam J, Ekindjian OG, Borderie D. Effects of repeated infliximab therapy on serum lipid profile in patients with refractory rheumatoid arthritis. Clinica Chimica Acta. 2006; 365(1-2):143-8.

116. Vis M, Nurmohamed MT, Wolbink G, Voskuyl AE, de Koning M, van de SR, et al. Short term effects of infliximab on the lipid profile in patients with rheumatoid arthritis. Journal of Rheumatolog. 2005; 32(2):252-5.

117. Popa C, Netea MG, Radstake T, Van der Meer JW, Stalenhoef AF, van Riel PL, et al. Influence of anti-tumour necrosis factor therapy on cardiovascular risk factors in patients with active rheumatoid arthritis. Annals of the Rheumatic Diseases. 2005; 64(2):303-5.

118. Peters MJ, Vis M, van Halm VP, Wolbink GJ, Voskuyl AE, Lems WF, et al. Changes in lipid profile during infliximab and corticosteroid treatment in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2007; 66(7):958-61.

119. Popa C, van den Hoogen FH, Radstake TR, Netea MG, Eijsbouts AE, den Heijer M, et al. Modulation of lipoprotein plasma concentrations during long-term anti-TNF therapy in patients with active rheumatoid arthritis. Annals of the Rheumatic Diseases. 2007; 66(11):1503-7.

120. Rossner S, Lofmark C. Dyslipoproteinaemia in patients with active, chronic polyarthritis. A study on serum lipoproteins and triglyceride clearance (intravenous fat tolerance test). Atherosclerosis. 1977; 28(1):41-52.

121. Vermont CL, den Brinker M, Kakeci N, de Kleijn ED, de Rijke YB, Joosten KFM, et al. Serum lipids and disease severity in children with severe meningococcal sepsis. Critical Care Medicine. 2005;33(7):1610-5.

122. Alexopoulos CG, Pournaras S, Vaslamatzis M, Avgerinos A, Raptis S. Changes in serum lipids and lipoproteins in cancer patients during chemotherapy. Cancer Chemotherapy & Pharmacology. 1992; 30(5):412-6.

123. Akgun S, Ertel NH, Mosenthal A, Oser W. Postsurgical reduction of serum lipoproteins: Interleukin-6 and the acute-phase response. Journal of Laboratory and Clinical Medicine. 1998;131 (1):103-8.

124. Hahn BH, Grossman J, Ansell BJ, Skaggs BJ, McMahon M. Altered lipoprotein metabolism in chronic inflammatory states: proinflammatory high-density lipoprotein and accelerated atherosclerosis in systemic lupus erythematosus and rheumatoid arthritis. Arthritis Research & Therapy. 2008; 10(4):213.

125. Popa C, van Tits LJH, Barrera P, Lemmers HLM, van den Hoogen FHJ, van Riel PLCM, et al. Anti-inflammatory therapy with tumour necrosis factor alpha inhibitors improves high-density lipoprotein cholesterol antioxidative capacity in rheumatoid arthritis patients. Annals of the Rheumatic Diseases. 2009; 68(6):868-72.

126. Choy E, Sattar N. Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. Annals of the Rheumatic Diseases. 2009; 68(4):460-9.

127. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. New England Journal of Medicine. 1995 ;333(20):1301-7.

128. McCarey DW, McInnes IB, Madhok R, Hampson R, Scherbakov O, Ford I, et al. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet. 2004; 363(9426):2015-21.

129. Jick SS, Choi H, Li L, McInnes IB, Sattar N. Hyperlipidaemia, statin use and the risk of developing rheumatoid arthritis. Annals of the Rheumatic Diseases. 2009; 68(4):546-51.

130. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Jr., Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New England Journal of Medicine. 2008; 359(21):2195-207.

131. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet. 2005; 366(9497):1640-9.

132. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet. 2006; 368(9536):666-78.

133. Stavropoulos-Kalinoglou A, Metsios GS, Smith JP, Panoulas VF, Douglas KMJ, Jamurtas AZ, et al. What predicts obesity in patients with rheumatoid arthritis? An investigation of the interactions between lifestyle and inflammation. International Journal of Obesity. 2010;34(2):295-301.

134. Stavropoulos-Kalinoglou A, Metsios GS, Panoulas VF, Douglas KMJ, Nevill AM, Jamurtas AZ, et al. Associations of obesity with modifiable risk factors for the development of cardiovascular disease in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2009; 68(2):242-5.

135. Stavropoulos-Kalinoglou A, Metsios GS, Koutedakis Y, Nevill AM, Douglas KM, Jamurtas A, et al. Redefining overweight and obesity in rheumatoid arthritis patients. Annals of the Rheumatic Diseases. 2007; 66(10):1316-21.

136. Bensimhon DR, Kraus WE, Donahue MP. Obesity and physical activity: a review. American Heart Journal. 2006; 151(3):598-603.

137. Stefanick ML, Mackey S, Sheehan M, Ellsworth N, Haskell WL, Wood PD. Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. New England Journal of Medicine. 1998; 339(1):12-20.

138. Wallberg-Henriksson H, Rincon J, Zierath JR. Exercise in the management of non-insulin-dependent diabetes mellitus. Sports Medicine. 1998;25 (1):25-35.

139. Sesso HD, Paffenbarger RS, Jr., Lee IM. Physical activity and coronary heart disease in men: The Harvard Alumni Health Study. Circulation. 2000; 29;102(9):975-80.

140. Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta-analysis: secondary prevention programs for patients with coronary artery disease. Annals of Internal Medicine. 2005; 143(9):659-72.

141. Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJ, Treharne GJ, Panoulas VF, Douglas KM, et al. Rheumatoid arthritis, cardiovascular disease and physical exercise: a systematic review. Rheumatology. 2008; 47(3):239-48.

142. Puig JG, Martinez MA. Hyperuricemia, gout and the metabolic syndrome. Current Opinion in Rheumatology. 2008; 20(2):187-91.

143. Atdjian M, Fernandez-Madrid F. Coexistence of chronic tophaceous gout and rheumatoid arthritis. Journal of Rheumatology. 1981;8 (6):989-92.

144. Panoulas VF, Milionis HJ, Douglas KM, Nightingale P, Kita MD, Klocke R, et al. Association of serum uric acid with cardiovascular disease in rheumatoid arthritis. Rheumatology. 2007; 46(9):1466-70.

145. Panoulas VF, Douglas KMJ, Milionis HJ, Nightingale P, Kita MD, Klocke R, et al. Serum uric acid is independently associated with hypertension in patients with rheumatoid arthritis. Journal of Human Hypertension. 2008; 22(3):177-82.

146. Mazzali M, Kanellis J, Han L, Feng L, Xia Y-Y, Chen Q, et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. American Journal of Physiology and Renal Physiology. 2002;282(6):F991-7.

147. Daoussis D, Panoulas V, Toms T, John H, Antonopoulos I, Nightingale P, et al. Uric acid is a strong independent predictor of renal dysfunction in patients with rheumatoid arthritis. Arthritis Research & Therapy. 2009;11(4):R116.

148. van Sijl AM, van den Oever IAM, Peters MJL, Boers M, Dijkmans BAC, van Halm VP, et al. Subclinical renal dysfunction is independently associated with cardiovascular events in rheumatoid arthritis: the CARRÉ Study. Annals of the Rheumatic Diseases. 2012; 71:341-4

149. Daoussis D, Panoulas VF, Antonopoulos I, John H, Toms TE, Wong P, et al. Cardiovascular risk factors and not disease activity, severity or therapy associate with renal dysfunction in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2010; 69(3):517-21.

150. Jacobsson LTH, Turesson C, Gulfe A, Kapetanovic MC, Petersson IF, Saxne T, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. Journal of Rheumatology. 2005; 32(7):1213-1218

151. Dixon WG, Watson KD, Lunt M, Hyrich KL, British Society for Rheumatology Biologics Register Control Centre C, Silman AJ, et al. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Arthritis & Rheumatism. 2007; 56(9):2905-12.

152. Dixon WG, Watson KD, Lunt M, Hyrich KL, Silman AJ, Symmons DPM. Rates of myocardial infarction and cerebrovascular accident are reduced in patients with rheumatoid arthritis treated with anti-TNF therapy compared to those treated with traditional DMARDS: results from the BSR biologics register Annals of the Rheumatic Diseases. 2006;65(Suppl II):109.

153. Peters MJL, Symmons DPM, McCarey D, Dijkmans BAC, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Annals of the Rheumatic Diseases. 2010; 69(2):325-31.

154. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. New England Journal of Medicine. 2011; 365(23):2205-19.

155. Cheng X, Yu X, Ding YJ, Fu QQ, Xie JJ, Tang TT, et al. The Th17/Treg imbalance in patients with acute coronary syndrome. Clinical Immunology. 2008; 127(1):89-97.

156. Pasceri V, Yeh ET. A tale of two diseases: atherosclerosis and rheumatoid arthritis. Circulation. 1999; 100(21):2124-6.

157. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W, Jr., et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation. 1995; 92(5):1355-74.

158. Mann JM, Davies MJ. Vulnerable plaque. Relation of characteristics to degree of stenosis in human coronary arteries. Circulation. 1996;94(5):928-31.

159. Hansel S, Lassig G, Pistrosch F, Passauer J. Endothelial dysfunction in young patients with long-term rheumatoid arthritis and low disease activity. Atherosclerosis. 2003; 170(1):177-80.

160. Booth AD, Jayne DR, Kharbanda RK, McEniery CM, Mackenzie IS, Brown J, et al. Infliximab improves endothelial dysfunction in systemic vasculitis: a model of vascular inflammation. Circulation. 2004; 109(14):1718-23.

161. Hurlimann D, Forster A, Noll G, Enseleit F, Chenevard R, Distler O, et al. Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. Circulation. 2002; 106(17):2184-7.

162. Irace C, Mancuso G, Fiaschi E, Madia A, Sesti G, Gnasso A. Effect of anti TNFalpha therapy on arterial diameter and wall shear stress and HDL cholesterol.. Atherosclerosis. 2004; 177(1):113-8.

163. Dessein PH, Joffe BI, Singh S. Biomarkers of endothelial dysfunction, cardiovascular risk factors and atherosclerosis in rheumatoid arthritis. Arthritis Research & Therapy. 2005; 7(3):R634-43.

164. Galarraga B, Khan F, Kumar P, Pullar T, Belch JJF. C-reactive protein: The underlying cause of microvascular dysfunction in rheumatoid arthritis. Rheumatology. 2008 47(12):1780-1784.

165. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension. 2001; 37(5):1236-41.

166. Wilkinson IB, Hall IR, MacCallum H, Mackenzie IS, McEniery CM, van der Arend BJ, et al. Pulse-wave analysis: clinical evaluation of a noninvasive, widely applicable method for assessing endothelial function. Arteriosclerosis, Thrombosis & Vascular Biology. 2002; 22(1):147-52.

167. Maki-Petaja KM, Hall FC, Booth AD, Wallace SM, Yasmin, Bearcroft PW, et al. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-alpha therapy. Circulation. 2006; 114(11):1185-92.

168. Avalos I, Chung CP, Oeser A, Gebretsadik T, Shintani A, Kurnik D, et al. Increased augmentation index in rheumatoid arthritis and its relationship to coronary artery atherosclerosis. Journal of Rheumatology. 2007; 34(12):2388-94.

169. Galarraga B, Khan F, Kumar P, Pullar T, Belch JJF. Etanercept improves inflammation-associated arterial stiffness in rheumatoid arthritis. Rheumatology. 2009;48(11):1418-23.

170. Galarraga B, Belch JJF, Pullar T, Ogston S, Khan F. Clinical improvement in rheumatoid arthritis is associated with healthier microvascular function in patients who respond to antirheumatic therapy. Journal of Rheumatology. 2010; 37(3):521-8.

171. Van Doornum S, McColl G, Jenkins A, Green DJ, Wicks IP. Screening for atherosclerosis in patients with rheumatoid arthritis: comparison of two in vivo tests of vascular function. Arthritis & Rheumatism. 2003; 48(1):72-80.

172. Wong M, Oakley SP, Young L, Jiang BY, Wierzbicki A, Panayi G, et al. Infliximab improves vascular stiffness in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2009; 68(8):1277-84.

173. Bots ML, Hofman A, de Jong PT, Grobbee DE. Common carotid intima-media thickness as an indicator of atherosclerosis at other sites of the carotid artery. The Rotterdam Study. Annals of Epidemiology. 1996; 6(2):147-53.

174. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation. 1997; 96(5):1432-7.

175. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. New England Journal of Medicine. 1999; 340(1):14-22.

176. Park YB, Ahn CW, Choi HK, Lee SH, In BH, Lee HC, et al. Atherosclerosis in rheumatoid arthritis: morphologic evidence obtained by carotid ultrasound. Arthritis & Rheumatism. 2002; 46(7):1714-9.

177. Kumeda Y, Inaba M, Goto H, Nagata M, Henmi Y, Furumitsu Y, et al. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. Arthritis & Rheumatism. 2002; 46(6):1489-97.

178. Gonzalez-Juanatey C, Llorca J, Amigo-Diaz E, Dierssen T, Martin J, Gonzalez-Gay MA. High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. Arthritis & Rheumatism. 2007; 57(6):1074-80.

179. Roman MJ, Shanker BA, Davis A, Lockshin MD, Sammaritano L, Simantov R, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. New England Journal of Medicine. 2003; 349(25):2399-406. [erratum appears in New England Journal of Medicine. 2006; 355(16):1746].

180. Vaudo G, Bocci EB, Shoenfeld Y, Schillaci G, Wu R, Del Papa N, et al. Precocious intima-media thickening in patients with primary Sjogren's syndrome. Arthritis & Rheumatism. 2005; 52(12):3890-7.

181. del Rincon I, Williams K, Stern MP, Freeman GL, O'Leary DH, Escalante A. Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. Arthritis & Rheumatism. 2003; 48(7):1833-40.

182. Sodergren A, Karp K, Boman K, Eriksson C, Lundstrom E, Smedby T, et al. Atherosclerosis in early rheumatoid arthritis: very early endothelial activation and rapid progression of intima media thickness. Arthritis Research & Therapy. 2010;12:R158.

183. Del Porto F, Lagana B, Lai S, Nofroni I, Tinti F, Vitale M, et al. Response to anti-tumour necrosis factor alpha blockade is associated with reduction of carotid intima-media thickness in patients with active rheumatoid arthritis. Rheumatology. 2007; 46(7):1111-5.

184. Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C, American Heart A, et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation. 2004; 109(3):433-8.

185. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005; 365(9468):1415-28.

186. Dessein PH, Joffe BI. Insulin resistance and impaired beta cell function in rheumatoid arthritis. Arthritis & Rheumatism. 2006; 54(9):2765-75.

187. Dessein PH, Joffe BI, Stanwix AE, Christian BF, Veller M. Glucocorticoids and insulin sensitivity in rheumatoid arthritis. Journal of Rheumatology. 2004; 31(5):867-74.

188. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. Journal of Clinical Investigation. 1995; 95(5):2409-15.

189. Dandona P, Weinstock R, Thusu K, Abdel-Rahman E, Aljada A, Wadden T. Tumor necrosis factor-alpha in sera of obese patients: fall with weight loss. Journal of Clinical Endocrinology & Metabolism. 1998; 83(8):2907-10.

190. Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010; 375(9709):132-40.

191. Goodson NJ, Symmons DP, Scott DG, Bunn D, Lunt M, Silman AJ. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year followup study of a primary care-based inception cohort. Arthritis & Rheumatism. 2005; 52(8):2293-9.

192. Giles JT, Bartlett SJ, Andersen R, Thompson R, Fontaine KR, Bathon JM. Association of body fat with C-reactive protein in rheumatoid arthritis. Arthritis and Rheumatism. 2008; 58 (9):2632-41.

193. Goodson NJ, Wiles NJ, Lunt M, Barrett EM, Silman AJ, Symmons DP. Mortality in early inflammatory polyarthritis: cardiovascular mortality is increased in seropositive patients. Arthritis & Rheumatism. 2002; 46(8):2010-9.

194. Liang KP, Kremers HM, Crowson CS, Snyder MR, Therneau TM, Roger VL, et al. Autoantibodies and the risk of cardiovascular events. Journal of Rheumatology. 2009;36 (11):2462-9.

195. Gerli R, Bartoloni Bocci E, Sherer Y, Vaudo G, Moscatelli S, Shoenfeld Y. Association of anti-cyclic citrullinated peptide antibodies with subclinical atherosclerosis in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2008; 67(5):724-5.

196. Farragher TM, Goodson NJ, Naseem H, Silman AJ, Thomson W, Symmons D, et al. Association of the HLA-DRB1 gene with premature death, particularly from cardiovascular disease, in patients with rheumatoid arthritis and inflammatory polyarthritis. Arthritis & Rheumatism. 2008; 58(2):359-69.

197. Chen Y, Dawes PT, Packham JC, Mattey DL. Interaction between smoking and functional polymorphism in the TGFB1 gene is associated with ischaemic heart disease and myocardial infarction in patients with rheumatoid arthritis: A cross-sectional study: Arthritis Research and Therapy.2012;14 (2): R81.

198. Panoulas VF, Stavropoulos-Kalinoglou A, Metsios GS, Smith JP, Milionis HJ, Douglas KMJ, et al. Association of interleukin-6 (IL-6)-174G/C gene polymorphism with cardiovascular disease in patients with rheumatoid arthritis: the role of obesity and smoking. Atherosclerosis. 2009;204(1):178-83.

199. Panoulas VF, Douglas KMJ, Smith JP, Stavropoulos-Kalinoglou A, Metsios GS, Nightingale P, et al. Transforming growth factor-beta1 869T/C, but not interleukin-6 -174G/C, polymorphism associates with hypertension in rheumatoid arthritis. Rheumatology. 2009; 48(2):113-8.

200. Panoulas VF, Douglas KMJ, Smith JP, Taffe P, Stavropoulos-Kalinoglou A, Toms TE, et al. Polymorphisms of the endothelin-1 gene associate with hypertension in patients with rheumatoid arthritis. Endothelium. 2008;15(4):203-12.

201. NICE. Clinical guidance 67. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. 2008; Available from: http://publications.nice.org.uk/lipid-modification-cg67.

202. Berger JS, Jordan CO, Lloyd-Jones D, Blumenthal RS. Screening for cardiovascular risk in asymptomatic patients. Journal of the American College of Cardiology. 2010; 55(12):1169-77.

203. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. American Heart Journal. 1991;121(1 Pt 2):293-8.

204. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998; 97(18):1837-47.

205. Tunstall-Pedoe H, Woodward M, estimation Sgor. By neglecting deprivation, cardiovascular risk scoring will exacerbate social gradients in disease. Heart. 2006; 92(3):307-10.

206. Woodward M, Brindle P, Tunstall-Pedoe H, estimation Sgor. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart. 2007; 93(2):172-6.

207. Cooney MT, Dudina AL, Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk: a review for clinicians. Journal of the American College of Cardiology. 2009; 54(14):1209-27.

208. National Cholesterol Education Program. Risk assessment tool for estimating 10-year risk of developing hard CHD (myocardial infarction and coronary death). Available from: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof.

209. ASSIGN score - prioritising prevention of cardiovascular disease; estimate the risk. Available from: http://assign-score.com/estimate-the-risk/.

210. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. British Medical Journal. 2008; 336(7659):1475-82.

211. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. British Medical Journal.2007; 335(7611):136.

212. European Society of Cardiology. SCORE risk charts. Available from: http://www.escardio.org/communities/EACPR/toolbox/health-professionals/Pages/SCORE-Risk-Charts.aspx.

213. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. New England Journal of Medicine. 1999; 340(24):1888-99.
[erratum appears in New England Journal of Medicine 1999 Aug 12;341(7):548].

214. Singh G. Treatment options for osteoarthritis. Surgical Technology International. 2003; 11:287-92.

215. British National Formulary. 62 ed: BMJ Group and Pharmaceutical Press; 2011.

216. Kurumbail RG, Stevens AM, Gierse JK, McDonald JJ, Stegeman RA, Pak JY, et al. Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents. Nature. 1996;384 (6610):644-8.

217. Brune K, Renner B, Hinz B. Using pharmacokinetic principles to optimize pain therapy. Nature Reviews Rheumatology. 2010; 6(10):589-98.

218. Vane J, Botting R. Inflammation and the mechanism of action of anti-inflammatory drugs. FASEB Journal. 1987;1 (2):89-96.

219. Hinz B, Brune K. Cyclooxygenase-2 - 10 Years later. Journal of Pharmacology and Experimental Therapeutics. 2002;300 (2):367-75.

20. FitzGerald GA. Coxibs and cardiovascular disease. New England Journal of Medicine. 2004; 351(17):1709-11.

221. Shi S, Klotz U. Clinical use and pharmacological properties of selective COX-2 inhibitors. European Journal of Clinical Pharmacology.2008;64(3):233-52.

222. Emery P, Zeidler H, Kvien TK, Guslandi M, Naudin R, Stead H, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. Lancet. 1999; 354(9196):2106-11.

223. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: Systematic review of randomised controlled trials. British Medical Journal. 2002; 325(7365):619-623

224. Burch JW, Stanford N, Majerus PW. Inhibition of platelet prostaglandin synthetase by oral aspirin. Journal of Clinical Investigation. 1978; 61(2):314-9.

225. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. New England Journal of Medicine. 2001; 345(25):1809-17.

226. Administration USFaD. Information for healthcare professionals: concomitant use of ibuprofen and aspirin. 2006; Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125222.htm.

227. Wilner KD, Rushing M, Walden C, Adler R, Eskra J, Noveck R, et al. Celecoxib does not affect the antiplatelet activity of aspirin in healthy volunteers. Journal of Clinical Pharmacology. 2002; 42(9):1027-30.

228. Cox ER, Frisse M, Behm A, Fairman KA. Over-the-counter pain reliever and aspirin use within a sample of long-term cyclooxygenase 2 users. Archives of Internal Medicine. 2004; 164(11):1243-6.

229. Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults. Annals of Internal Medicine. 2005; 142(7):481-9.

230. Goldstein JL, Cryer B, Amer F, Hunt B. Celecoxib plus aspirin versus naproxen and lansoprazole plus aspirin: a randomized, double-blind, endoscopic trial. Clinical Gastroenterology & Hepatology. 2007; 5(10):1167-74.

231. Strand V. Are COX-2 inhibitors preferable to non-selective non-steroidal anti-inflammatory drugs in patients with risk of cardiovascular events taking low-dose aspirin? Lancet. 2008; 370(9605):2138-51.

232. Rahme E, Nedjar H. Risks and benefits of COX-2 inhibitors vs non-selective NSAIDs: does their cardiovascular risk exceed their gastrointestinal benefit? A retrospective cohort study. Rheumatology. 2007; 46(3):435-8.

233. Rahme E, Bardou M, Dasgupta K, Toubouti Y, Ghosn J, Barkun AN. Hospitalization for gastrointestinal bleeding associated with non-steroidal anti-inflammatory drugs among elderly patients using low-dose aspirin: a retrospective cohort study. Rheumatology. 2007; 46(2):265-72.

234. Hernandez-Diaz S, Varas-Lorenzo C, Garcia Rodriguez LA. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. Basic & Clinical Pharmacology & Toxicology. 2006; 98(3):266-74.

235. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. British Medical Journal. 2006; 332(7553):1302-5.

236. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. Journal of the American Medical Association. 2006; 296(13):1633-44.

237. Singh G, Wu O, Langhorne P, Madhok R. Risk of acute myocardial infarction with nonselective non-steroidal anti-inflammatory drugs: a meta-analysis.[see comment]. Arthritis Research & Therapy. 2006; 8(5):R153.

238. Gislason GH, Jacobsen S, Rasmussen JN, Rasmussen S, Buch P, Friberg J, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. Circulation. 2006; 113(25):2906-13.

239. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. New England Journal of Medicine. 2000; 343(21):1520-8,

240. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. New England Journal of Medicine. 2005; 352(11):1092-102. [erratum appears in New England Journal of Med. 2006 Jul 13;355(2):221].

241. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. New England Journal of Medicine. 2005; 352(11):1071-80.

242. Agency USFaD. Questions and answers FDA regulatory actions for the COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106148.htm.

243. Agency EM. EMA concludes action on COX-2 inhibitors. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/01/news_detail_000969.jsp&mid=WC0b01ac058004d5c1&jsenabled=true.

244. Agency MaHPR. Cardiovascular safety of COX-2 inhibitors and non-selective NSAIDs. Available from: http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-A-F/CardiovascularsafetyofCOX-2inhibitorsandnon-selectiveNSAIDs/index.htm

245. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet. 2004; 364(9450):2021-9.

246. Solomon SD, Wittes J, Finn PV, Fowler R, Viner J, Bertagnolli MM, et al. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: the cross trial safety analysis. Circulation. 2008; 117(16):2104-13.

247. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet. 2006; 368(9549):1771-81.

248. Andersohn F, Suissa S, Garbe E. Use of first- and second-generation cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs and risk of acute myocardial infarction. Circulation. 2006; 113(16):1950-7.

249. White WB, Kent J, Taylor A, Verburg KM, Lefkowith JB, Whelton A. Effects of celecoxib on ambulatory blood pressure in hypertensive patients on ACE inhibitors. Hypertension. 2002; 39(4):929-34.

250. Harris CJ, Brater DC. Renal effects of cyclooxygenase-2 selective inhibitors. Current Opinion in Nephrology & Hypertension. 2001; 10(5):603-10.

251. Aisen PS, Schafer K, Grundman M, Thomas R, Thal LJ. NSAIDs and hypertension. Archives of Internal Medicine. 2003; 163(9):1115

252. Whelton A, Schulman G, Wallemark C, Drower EJ, Isakson PC, Verburg KM, et al. Effects of celecoxib and naproxen on renal function in the elderly. Archives of Internal Medicine. 2000; 160(10):1465-70.

253. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. Archives of Internal Medicine. 1993; 153(4):477-84.

254. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Annals of Internal Medicine. 1994; 121(4):289-300.

255. Singh G, Miller JD, Huse DM, Pettitt D, D'Agostino RB, Russell MW. Consequences of increased systolic blood pressure in patients with osteoarthritis and rheumatoid arthritis. Journal of Rheumatology. 2003; 30(4):714-9.

256. Davis BR. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). Journal of the American Medical Association. 2000; 283 (15):1967-75.

257. Morrison A, Ramey DR, van Adelsberg J, Watson DJ. Systematic review of trials of the effect of continued use of oral non-selective NSAIDs on blood pressure and hypertension. Current Medical Research & Opinion. 2007; 23(10):2395-404.

258. Wong DG, Spence JD, Lamki L, Freeman D, McDonald JW. Effect of non-steroidal anti-inflammatory drugs on control of hypertension by beta-blockers and diuretics. Lancet. 1986; 1(8488):997-1001.

259. Fogari R, Zoppi A, Carretta R, Veglio F, Salvetti A, Italian Collaborative Study G. Effect of indomethacin on the antihypertensive efficacy of valsartan and lisinopril: a multicentre study. Journal of Hypertension. 2002;20(5):1007-14.

260. Klassen DK, Jane LH, Young DY, Peterson CA. Assessment of blood pressure during naproxen therapy in hypertensive patients treated with nicardipine. American Journal of Hypertension. 1995; 8(2):146-53.

261. Morgan T, Anderson A. Interaction of indomethacin with felodipine and enalapril. Journal of Hypertension. 1993;11 (SUPPL. 5):S338-S9.

262. Aw TJ, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. Archives of Internal Medicine. 2005; 165(5):490-6.

263. Sowers JR, White WB, Pitt B, Whelton A, Simon LS, Winer N, et al. The Effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. Archives of Internal Medicine. 2005; 165(2):161-8. [erratum appears in Archives of Internal Medicine. 2005 Mar 14;165(5):551].

264. Wolfe F, Zhao S, Pettitt D. Blood pressure destabilization and edema among 8538 users of celecoxib, rofecoxib, and nonselective nonsteroidal antiinflammatory drugs (NSAID) and nonusers of NSAID receiving ordinary clinical care. Journal of Rheumatology. 2004; 31(6):1143-51.

265. Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. Journal of the American Medical Association. 2006; 296(13):1619-32.

266. Krum H, Swergold G, Curtis SP, Kaur A, Wang H, Smugar SS, et al. Factors associated with blood pressure changes in patients receiving diclofenac or etoricoxib: results from the MEDAL study. Journal of Hypertension.2009; 27(4):886-93.

267. Huerta C, Varas-Lorenzo C, Castellsague J, Garcia Rodriguez LA. Non-steroidal anti-inflammatory drugs and risk of first hospital admission for heart failure in the general population. Heart. 2006; 92(11):1610-5.

268. McGettigan P, Han P, Jones L, Whitaker D, Henry D. Selective COX-2 inhibitors, NSAIDs and congestive heart failure: differences between new and recurrent cases. British Journal of Clinical Pharmacology. 2008; 65(6):927-34.

269. Hudson M, Richard H, Pilote L. Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study. British Medical Journal. 2005; 330(7504):1370.

270. Mamdani M, Juurlink DN, Lee DS, Rochon PA, Kopp A, Naglie G, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. Lancet. 2004; 363(9423):1751-6.

271. Koseki Y, Terai C, Moriguchi M, Uesato M, Kamatani N. A prospective study of renal disease in patients with early rheumatoid arthritis. Annals of the Rheumatic Diseases. 2001; 60(4):327-31.

272. Unsworth J, Sturman S, Lunec J, Blake DR. Renal impairment associated with non-steroidal anti-inflammatory drugs. Annals of the Rheumatic Diseases. 1987; 46(3):233-6.

273. Nived O, Sturfelt G, Westling H, White T. Is serum creatinine concentration a reliable index of renal function in rheumatic diseases? British Medical Journal. 1983; 286(6366):684-5.

274. Adams DH, Howie AJ, Michael J, McConkey B, Bacon PA, Adu D. Non-steroidal anti-inflammatory drugs and renal failure. Lancet. 1986; 1(8472):57-60.

275. Harris RC. COX-2 and the kidney. Journal of Cardiovascular Pharmacology. 2006;47 Suppl 1:S37-42.

276. Stichtenoth DO, Marhauer V, Tsikas D, Gutzki F-M, Frolich JC. Effects of specific COX-2-inhibition on renin release and renal and systemic prostanoid synthesis in healthy volunteers. Kidney International. 2005; 68(5):2197-207.

277. Schwartz JI, Thach C, Lasseter KC, Miller J, Hreniuk D, Hilliard DA, et al. Effects of etoricoxib and comparator nonsteroidal anti-inflammatory drugs on urinary sodium excretion, blood pressure, and other renal function indicators in elderly subjects consuming a controlled sodium diet. Journal of Clinical Pharmacology. 2007; 47(12):1521-31.

278. Schoen RT, Vender RJ. Mechanisms of nonsteroidal anti-inflammatory drug-induced gastric damage. American Journal of Medicine. 1989; 86(4):449-58.

279. Lichtenstein DR, Syngal S, Wolfe MM. Nonsteroidal antiinflammatory drugs and the gastrointestinal tract. The double-edged sword. Arthritis & Rheumatism. 1995; 38(1):5-18.

280. Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. Archives of Internal Medicine. 2000; 160(14):2093-9.

281. Lanas A, Garcia-Rodriguez LA, Arroyo MT, Gomollon F, Feu F, Gonzalez-Perez A, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut. 2006; 55(12):1731-8.

282. Singh G, Triadafilopoulos G. Appropriate choice of proton pump inhibitor therapy in the prevention and management of NSAID-related gastrointestinal damage. International Journal of Clinical Practice. 2005; 59(10):1210-1217

283. Ibanez L, Vidal X, Vendrell L, Moretti U, Laporte JR, Spanish-Italian Collaborative Group for the Epidemiology of Gastrointestinal B. Upper gastrointestinal bleeding associated with antiplatelet drugs. Alimentary Pharmacology & Therapeutics. 2006; 23(2):235-42.

284. Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E, et al. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane database of systematic reviews. 2002;(4):CD002296.

285. Chan FK, Chung SC, Suen BY, Lee YT, Leung WK, Leung VK, et al. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. New England Journal of Medicine. 2001; 344(13):967-73.

286. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. Journal of the American Medical Association. 2000; 284(10):1247-55.

287. Singh G, Fort JG, Goldstein JL, Levy RA, Hanrahan PS, Bello AE, et al. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. American Journal of Medicine. 2006; 119(3):255-66.
[erratum appears in American Journal of Medicine. 2006 Sep;119(9):801].

288. Laine L, Curtis SP, Cryer B, Kaur A, Cannon CP, Committee MS. Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet. 2007; 369(9560):465-73.

289. Chan FK, Wong VW, Suen BY, Wu JC, Ching JY, Hung LC, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. Lancet. 2007; 369(9573):1621-6.

290. Arber N, Eagle CJ, Spicak J, Racz I, Dite P, Hajer J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. New England Journal of Medicine. 2006; 355(9):885-95.

291. Chan FKL, Lanas A, Scheiman J, Berger MF, Nguyen H, Goldstein JL. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. Lancet. 2010; 17;376(9736):173-9.

292. Andersohn F, Schade R, Suissa S, Garbe E. Cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs and the risk of ischemic stroke: a nested case-control study. Stroke. 2006; 37(7):1725-30.

293. Haag MD, Bos MJ, Hofman A, Koudstaal PJ, Breteler MM, Stricker BH. Cyclooxygenase selectivity of nonsteroidal anti-inflammatory drugs and risk of stroke. Archives of Internal Medicine. 2008; 168(11):1219-24.

294. Nadareishvili Z, Michaud K, Hallenbeck JM, Wolfe F. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case-control study. Arthritis & Rheumatism. 2008; 59(8):1090-6.

295. Roumie CL, Mitchel EF, Jr., Kaltenbach L, Arbogast PG, Gideon P, Griffin MR. Nonaspirin NSAIDs, cyclooxygenase 2 inhibitors, and the risk for stroke. Stroke. 2008; 39(7):2037-45.

296. Todd PA, Sorkin EM. Diclofenac sodium. A reappraisal of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs. 1988; 35(3):244-85.

297. O'Connor N, Dargan PI, Jones AL. Hepatocellular damage from non-steroidal anti-inflammatory drugs. Quarterly Journal of Medicine. 2003; 96(11):787-91.

298. Lapeyre-Mestre M, de Castro AM, Bareille MP, Del Pozo JG, Requejo AA, Arias LM, et al. Non-steroidal anti-inflammatory drug-related hepatic damage in France and Spain: analysis from national spontaneous reporting systems. Fundamental & Clinical Pharmacology. 2006;20(4):391-5.

299. Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. Lancet. 2004; 364(9435):665-74.

300. Farkouh ME, Kirshner H, Harrington RA, Ruland S, Verheugt FW, Schnitzer TJ, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. Lancet. 2004; 364(9435):675-84.

301. Medicines and Healthcare Products Regulatory Agency. Drug safety information: Lumiracoxib - suspension of UK licences with immediate effect. 2007; Available from: http://www.mhra.gov.uk/Publications/Safetywarnings/DrugAlerts/CON2033083

302. Sanchez-Matienzo D, Arana A, Castellsague J, Perez-Gutthann S. Hepatic disorders in patients treated with COX-2 selective inhibitors or nonselective NSAIDs: A case/noncase analysis of spontaneous reports. Clinical Therapeutics. 2006; 28(8):1123-1132

303. McKellar G, Madhok R, Singh G. Update on the use of analgesics versus nonsteroidal anti-inflammatory drugs in rheumatic disorders: Risks and benefits. Current Opinion in Rheumatology. 2008;20 (3):239-45.

304. Trichopoulou A. Mediterranean diet: the past and the present. Nutrition Metabolism & Cardiovascular Diseases. 2001; 11(4 Suppl):1-4.

305. Levenstein H. Revolution at the table; the transformation of the American diet. New York: Oxford; 1988.

306. Bolton-Smith C, Smith WC, Woodward M, Tunstall-Pedoe H. Nutrient intakes of different social-class groups: results from the Scottish Heart Health Study (SHHS). British Journal of Nutrition. 1991; 65(3):321-35.

307. Castelvetro C. The fruit, herbs and vegetables of Italy. London: Viking; 1989.

308. David E. A book of Mediterranean food. London: Penguin; 1998.

309. UNESCO. Forty six new elements added to representative list of the intangible cultural heritage. 2010; Available from: http://www.unesco.org/new/en/media-services/single-view/news/forty_six_new_elements_added_to_representative_list_of_the_intangible_cultural_heritage/.

310. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, Gnardellis C, Lagiou P, Polychronopoulos E, et al. Diet and overall survival in elderly people. British Medical Journal. 1995; 311(7018):1457-60.

311. Yarnell JWG, Fehily AM, Milbank JE. A short dietary questionnaire for use in an epidemiological survey: Comparison with weighed dietary records. Human Nutrition: Applied Nutrition. 1983; 37(2):103-12.

312. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. New England Journal of Medicine. 2003; 348(26):2599-608.

313. Knoops KT, de Groot LC, Kromhout D, Perrin AE, Moreiras-Varela O, Menotti A, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. Journal of the American Medical Association. 2004; 292(12):1433-9.

314. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. British Medical Journal 2008;337:a1344.

315. Lasheras C, Fernandez S, Patterson AM. Mediterranean diet and age with respect to overall survival in institutionalized, nonsmoking elderly people. American Journal of Clinical Nutrition. 2000; 71(4):987-92.

316. Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, et al. The diet and 15-year death rate in the seven countries study. American Journal of Epidemiology. 1986; 124(6):903-15.

317. Kromhout D, Keys A, Aravanis C, Buzina R, Fidanza F, Giampaoli S, et al. Food consumption patterns in the 1960s in seven countries. American Journal of Clinical Nutrition.1 989; 49(5):889-94.

318. Trichopoulou A. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. British Medical Journal. 2005; 330(7498):991-5.

319. Mitrou PN, Kipnis V, Thiebaut AC, Reedy J, Subar AF, Wirfalt E, et al. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health Study. Archives of Internal Medicine. 2007; 167(22):2461-8.

320. Kouris-Blazos A, Gnardellis C, Wahlqvist ML, Trichopoulos D, Lukito W, Trichopoulou A. Are the advantages of the Mediterranean diet transferable to other populations? A cohort study in Melbourne, Australia. British Journal of Nutrition. 1999; 82(1):57-61.

321. Harriss LR, English DR, Powles J, Giles GG, Tonkin AM, Hodge AM, et al. Dietary patterns and cardiovascular mortality in the Melbourne Collaborative Cohort Study. American Journal of Clinical Nutrition. 2007; 86(1):221-9.

322. Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, et al. Fish consumption and risk of sudden cardiac death. Journal of the American Medical Association. 1998; 279(1):23-8.

323. de Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet. 1994; 343(8911):1454-9.
[erratum appears in Lancet 1995 Mar 18;345(8951):738].

324. de Lorgeril M, Salen P, Martin JL, Mamelle N, Monjaud I, Touboul P, et al. Effect of a mediterranean type of diet on the rate of cardiovascular complications in patients with coronary artery disease. Insights into the cardioprotective effect of certain nutriments. Journal of the American College of Cardiology. 1996; 28(5):1103-8.

325. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation. 1999; 99(6):779-85.

326. de Lorgeril M, Salen P, Martin JL, Monjaud I, Boucher P, Mamelle N. Mediterranean dietary pattern in a randomized trial: prolonged survival and possible reduced cancer rate. Archives of Internal Medicine. 1998; 158(11):1181-7.

327. Marchioli R. Dietary supplementation with N-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. Lancet. 1999; 354(9177): 447-455.

328. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet.1989; 2(8666):757-61.

329. Kromhout D, Giltay EJ, Geleijnse JM, Alpha Omega Trial G. n-3 fatty acids and cardiovascular events after myocardial infarction. New England Journal of Medicine. 2010; 363(21):2015-26.

330. Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ruiz-Gutierrez V, Covas MI, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Annals of Internal Medicine. 2006; 145(1):1-11.

331. Alonso A, de la Fuente C, Martin-Arnau AM, de Irala J, Martinez JA, Martinez-Gonzalez MA. Fruit and vegetable consumption is inversely associated with blood pressure in a Mediterranean population with a high vegetable-fat intake: the Seguimiento Universidad de Navarra (SUN) Study. British Journal of Nutrition. 2004; 92(2):311-9.

332. Strazzullo P, Ferro-Luzzi A, Siani A, Scaccini C, Sette S, Catasta G, et al. Changing the Mediterranean diet: effects on blood pressure. Journal of Hypertension. 1986; 4(4):407-12.

333. Martinez-Gonzalez MA, Fuente-Arrillaga C, Nunez-Cordoba JM, Basterra-Gortari FJ, Beunza JJ, Vazquez Z, et al. Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. British Medical Journal. 2008; 336(7657):1348-51.

334. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Journal of the American Medical Association. 2001; 285(19):2486-97.

335. Alvarez Leon EE, Henriquez P, Serra-Majem L. Mediterranean diet and metabolic syndrome: a cross-sectional study in the Canary Islands. Public Health Nutrition. 2006; 9(8A):1089-98.

336. Karvounaris SA, Sidiropoulos PI, Papadakis JA, Spanakis EK, Bertsias GK, Kritikos HD, et al. Metabolic syndrome is common among middle-to-older aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: a retrospective, cross-sectional, controlled, study. Annals of the Rheumatic Diseases. 2007; 66(1):28-33.

337. Fito M, Guxens M, Corella D, Saez G, Estruch R, de la TR, et al. Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. Archives of Internal Medicine. 2007; 167(11):1195-203.

338. Lapointe A, Goulet J, Couillard C, Lamarche B, Lemieux S. A nutritional intervention promoting the Mediterranean food pattern is associated with a decrease in circulating oxidized LDL particles in healthy women from the Quebec City metropolitan area. Journal of Nutrition. 2005; 135(3):410-5.

339. Fuentes F, Lopez-Miranda J, Sanchez E, Sanchez F, Paez J, Paz-Rojas E, et al. Mediterranean and low-fat diets improve endothelial function in hypercholesterolemic men. Annals of Internal Medicine. 2001; 134(12):1115-9.

340. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, et al. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. Journal of the American Medical Association. 2004; 292(12):1440-6.

341. Chrysohoou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C. Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: The ATTICA Study. Journal of the American College of Cardiology. 2004; 44(1):152-8.

342. Kang JX, Leaf A. Prevention of fatal cardiac arrhythmias by polyunsaturated fatty acids. American Journal of Clinical Nutrition. 2000; 71(1 Suppl):202S-7S.

343. Linos A, Kaklamani VG, Kaklamani E, Koumantaki Y, Giziaki E, Papazoglou S, et al. Dietary factors in relation to rheumatoid arthritis: a role for olive oil and cooked vegetables? American Journal of Clinical Nutrition. 1999; 70(6):1077-82. [erratum appears in Am J Clin Nutr 2000 Apr;71(4):1010].

344. Pattison DJ, Silman AJ, Goodson NJ, Lunt M, Bunn D, Luben R, et al. Vitamin C and the risk of developing inflammatory polyarthritis: prospective nested case-control study. Annals of the Rheumatic Diseases. 2004; 63(7):843-7.

345. Pattison DJ, Symmons DP, Lunt M, Welch A, Luben R, Bingham SA, et al. Dietary risk factors for the development of inflammatory polyarthritis: evidence for a role of high level of red meat consumption. Arthritis & Rheumatism. 2004; 50(12):3804-12.

346. Skoldstam L, Hagfors L, Johansson G. An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2003; 62(3):208-14.

347. Hafstrom I, Ringertz B, Spangberg A, von Zweigbergk L, Brannemark S, Nylander I, et al. A vegan diet free of gluten improves the signs and symptoms of rheumatoid arthritis: the effects on arthritis correlate with a reduction in antibodies to food antigens.[see comment]. Rheumatology. 2001; 40(10):1175-9.

348. Beauchamp GK, Keast RS, Morel D, Lin J, Pika J, Han Q, et al. Phytochemistry: ibuprofen-like activity in extra-virgin olive oil. Nature. 2005; 437(7055):45-6.

349. Nishimoto N. Interleukin-6 in rheumatoid arthritis. Current Opinion in Rheumatology. 2006; 18(3):277-81.

350. Harris TB, Ferrucci L, Tracy RP, Corti MC, Wacholder S, Ettinger WH, Jr., et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. American Journal of Medicine. 1999; 106(5):506-12.

351. Dai J, Miller AH, Bremner JD, Goldberg J, Jones L, Shallenberger L, et al. Adherence to the mediterranean diet is inversely associated with circulating interleukin-6 among middle-aged men: a twin study. Circulation. 2008; 117(2):169-75.

352. Salas-Salvado J, Garcia-Arellano A, Estruch R, Marquez-Sandoval F, Corella D, Fiol M, et al. Components of the mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease. European Journal of Clinical Nutrition. 2008; 62(5):651-659.

353. Caughey GE, Mantzioris E, Gibson RA, Cleland LG, James MJ. The effect on human tumor necrosis factor alpha and interleukin 1 beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. American Journal of Clinical Nutrition. 1996; 63(1):116-22.

354. Manson JE, Gaziano JM, Jonas MA, Hennekens CH. Antioxidants and cardiovascular disease: a review. Journal of the American College of Nutrition. 1993; 12(4):426-32.

355. Hughes DA, Pinder AC, Piper Z, Johnson IT, Lund EK. Fish oil supplementation inhibits the expression of major histocompatibility complex class II molecules and adhesion molecules on human monocytes. American Journal of Clinical Nutrition. 1996; 63(2):267-72.

356. Belch JJF, Ansell D, Madhok R, O'Dowd A, Sturrock RD. Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: A double blind placebo controlled study. Annals of the Rheumatic Diseases. 1988;47 (2):96-104.

357. Kremer JM, Lawrence DA, Petrillo GF, Litts LL, Mullaly PM, Rynes RI, et al. Effects of high-dose fish oil on rheumatoid arthritis after stopping nonsteroidal antiinflammatory drugs. Clinical and immune correlates. Arthritis & Rheumatism. 1995;38(8):1107-14.

358. Galarraga B, Ho M, Youssef HM, Hill A, McMahon H, Hall C, et al. Cod liver oil (n-3 fatty acids) as an non-steroidal anti-inflammatory drug sparing agent in rheumatoid arthritis. Rheumatology. 2008; 47(5):665-9.

359. Cleland LG, Caughey GE, James MJ, Proudman SM. Reduction of cardiovascular risk factors with longterm fish oil treatment in early rheumatoid arthritis.[see comment]. Journal of Rheumatology. 2006; 33(10):1973-9.

360. Hill C, Gill TK, Appleton S, Cleland LG, Taylor AW, Adams RJ. The use of fish oil in the community: results of a population-based study. Rheumatology. 2009;48(4):441-2.

361. Shapiro JA, Koepsell TD, Voigt LF, Dugowson CE, Kestin M, Nelson JL. Diet and rheumatoid arthritis in women: a possible protective effect of fish consumption. Epidemiology. 1996; 7(3):256-63.

362. Mendez MA, Popkin BM, Jakszyn P, Berenguer A, Tormo MJ, Sanchez MJ, et al. Adherence to a Mediterranean diet is associated with reduced 3-year incidence of obesity. Journal of Nutrition. 2006; 136(11):2934-8.

363. Bastard JP, Jardel C, Bruckert E, Blondy P, Capeau J, Laville M, et al. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. Journal of Clinical Endocrinology & Metabolism. 2000; 85(9):3338-42.

364. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. New England Journal of Medicine. 2008;359 (3):229-41.

365. Skoldstam L, Brudin L, Hagfors L, Johansson G. Weight reduction is not a major reason for improvement in rheumatoid arthritis from lacto-vegetarian, vegan or Mediterranean diets. Nutrition Journal. 2005; 4:15.

366. Cottet V, Touvier M, Fournier A, Touillaud MS, Lafay L, Clavel-Chapelon F, et al. Postmenopausal breast cancer risk and dietary patterns in the E3N-EPIC prospective cohort study. American Journal of Epidemiology. 2009; 170(10):1257-67.

367. Buckland G, Agudo A, Lujan L, Jakszyn P, Bueno-de-Mesquita HB, Palli D, et al. Adherence to a Mediterranean diet and risk of gastric adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. American Journal of Clinical Nutrition. 2010; 91(2):381-90.

368. Barros R, Moreira A, Fonseca J, de Oliveira JF, Delgado L, Castel-Branco MG, et al. Adherence to the Mediterranean diet and fresh fruit intake are associated with improved asthma control. Allergy. 2008; 63(7):917-23.

369. Chatzi L, Apostolaki G, Bibakis I, Skypala I, Bibaki-Liakou V, Tzanakis N, et al. Protective effect of fruits, vegetables and the Mediterranean diet on asthma and allergies among children in Crete. Thorax. 2007; 62(8):677-83.

370. Hanlon P, Lawder RS, Buchanan D, Redpath A, Walsh D, Wood R, et al. Why is mortality higher in Scotland than in England and Wales? Decreasing influence of socioeconomic deprivation between 1981 and 2001 supports the existence of a 'Scottish Effect'. Journal of Public Health. 2005; 27(2):199-204.

371. Wrieden WL, Connaghan J, Morrison C, Tunstall-Pedoe H. Secular and socio-economic trends in compliance with dietary targets in the north Glasgow MONICA population surveys 1986-1995: did social gradients widen? Public Health Nutrition. 2004; 7(7):835-42.

372. The Scottish Diet: Report of a working party to the Chief Medical Officer for Scotland and London. editor: HMSO; 1993.

373. Papadaki A, Scott JA. The Mediterranean Eating in Scotland Experience project: Evaluation of an Internet-based intervention promoting the Mediterranean diet. British Journal of Nutrition. 2005; 94(2): 290-298.

374. Scottish Health Survey 2008. The Scottish Government; 2009; Available from: www.scotland.gov.uk/Publications/2009/09/28102003/0.

375. Townsend P, Phillimore P, Beattie A. Health and deprivation: inequality and the North: Croom Helm; 1988.

376. Carstairs V, Morris R. Deprivation and Health in Scotland. Aberdeen: Aberdeen University Press; 1991.

377. Scottish Index of Multiple Deprivation. Available from: www.scotland.gov.uk/Topics/Statistics/SIMD.

378. Maiden N, Capell HA, Madhok R, Hampson R, Thomson EA. Does social disadvantage contribute to the excess mortality in rheumatoid arthritis patients? Annals of the Rheumatic Diseases. 1999; 58(9):525-9.

379. McEntegart A, Morrison E, Capell HA, Duncan MR, Porter D, Madhok R, et al. Effect of social deprivation on disease severity and outcome in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 1997; 56(7):410-3.

380. Young A, Wilkinson P, Talamo J, Dixey J, Jones R, Hunt A, et al. Socioeconomic deprivation and rheumatoid disease: what lessons for the health service? ERAS Study Group. Early Rheumatoid Arthritis Study. Annals of the Rheumatic Diseases. 2000; 59(10):794-9.

381. Singh-Manoux A, Nabi H, Shipley M, Gueguen A, Sabia S, Dugravot A, et al. The role of conventional risk factors in explaining social inequalities in coronary heart disease: the relative and absolute approaches to risk. Epidemiology. 2008;19(4):599-605.

382. O'Flaherty M, Bishop J, Redpath A, McLaughlin T, Murphy D, Chalmers J, et al. Coronary heart disease mortality among young adults in Scotland in relation to social inequalities: time trend study. British Medical Journal. 2009; 339:b2613

383. Association WM. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Available from: http://www.wma.net/en/30publications/10policies/b3/.

384. McWilliams C, Johnstone C, Mooney G. Urban policy in the New Scotland: the roles of social inclusion partnerships. Space and Polity.2004; 8(3):309-19.

385. Scotland C. An overview of the Social Inclusion Partnership (SIP) programme. 2006; Available from: www.scotland.gov.uk/Resource/Doc/1125/0086285.pdf.

386. Scott DL, Antoni C, Choy EH, Van Riel PCLM. Joint counts in routine practice. Rheumatology. 2003; 42(8):919-23.

387. van Riel PL, Reekers P, van de Putte LB, Gribnau FW. Association of HLA antigens, toxic reactions and therapeutic response to auranofin and aurothioglucose in patients with rheumatoid arthritis. Tissue Antigens. 1983; 22(3):194-9.

388. van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Annals of the Rheumatic Diseases. 1990; 49(11):916-20.

389. Van Riel PL, Franssen R, DL S. EULAR Handbook of Clinical Assessment in Rheumatoid Arthritis. 3rd ed.

390. Anderson JJ, Chernoff MC. Sensitivity to change of rheumatoid arthritis clinical trial outcome measures. Journal of Rheumatology.1993; 20(3):535-7.

391. Ranganath VK, Yoon J, Khanna D, Park GS, Furst DE, Elashoff DA, et al. Comparison of composite measures of disease activity in an early seropositive rheumatoid arthritis cohort. Annals of the Rheumatic Diseases. 2007; 66(12):1633-40.

392. Ritchie DM, Boyle JA, McInnes JM, Jasani MK, Dalakos TG, Grieveson P, et al. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. Quarterly Journal of Medicine. 1968; 37(147):393-406.

393. van Riel PL, van Gestel AM. Clinical outcome measures in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2000; 59 Suppl 1:i28-31.

394. Bellamy N, Muirden KD, Brooks PM, Barraclough D, Tellus MM, Campbell J. A survey of outcome measurement procedures in routine rheumatology outpatient practice in Australia. Journal of Rheumatology. 1999; 26(7):1593-9.

395. The SF-12: an even shorter health survey. Available from: www.sf-36.org/tools/sf12.shtml.

396. Ware Jr J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Medical Care. 1996;34(3):220-33.

397. SF12v2 Health Survey. Available from: www.qualitymetric.com/demos/TP_Launch.aspx?SID=52304.

398. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis & Rheumatism. 1980; 23(2):137-45.

399. HAQ form. Available from: www.hqlo.com/content/supplementary/1477-7525-1-20-s1.pdf.

400. Hurst NP, Ruta DA, Kind P. Comparison of the MOS short form-12 (SF12) health status questionnaire with the SF36 in patients with rheumatoid arthritis. British Journal of Rheumatology. 1998; 37(8):862-9.

401. ASSIGN score. Prioritising prevention of cardiovascular disease - estimate the risk. Available from: http://assign-score.com/estimate-the-risk/.

402. The Renal Association. About eGFR. Available from: http://www.renal.org/whatwedo/InformationResources/CKDeGUIDE/AbouteGFR.aspx.

403. The Renal Association eguide. eGFR calculator. Available from: http://www.renal.org/eGFRcalc/GFR.pl.

404. Thompson FE, Subar AF. Dietary Assessment Methodology. Available from: http://riskfactor.cancer.gov/diet/adi/thompson_subar_dietary_assessment_methodology.pdf.

405. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion J-M, Mancia G, et al. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. Journal of Hypertension. 2003; 21(5):821-48.

406. British Hypertension Society. Blood pressure measurement with electronic blood pressure monitors. Available from: www.bhsoc.org/bp_monitors/BLOOD_PRESSURE_1784a.pdf

407. Scottish Executive. Scottish Index of Multiple Deprivation 2006: General Report. Edinburgh: Scottish Executive National Statistics Publication; 2006.

408. Capell HA, Madhok R, Porter DR, Munro RA, McInnes IB, Hunter JA, et al. Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from the double-blind placebo-controlled MASCOT study. Annals of the Rheumatic Diseases. 2007; 66(2):235-41.

409. Rosano GMC, Vitale C, Marazzi G, Volterrani M. Menopause and cardiovascular disease: the evidence. Climacteric. 2007; 10 Suppl 1:19-24.

410. Neustadt DH. Double blind evaluation of the long-term effects of etodolac versus ibuprofen in patients with rheumatoid arthritis. Journal of Rheumatology. 1997; 47 Suppl:17-22.

411. Spencer-Green G. Low dose etodolac in rheumatoid arthritis: a review of early studies. Journal of Rheumatology. 1997;47:3-9

412. Hawkey CJ. COX-2 inhibitors. Lancet. 1999; 353(9149):307-14.

413. Russell RI. COX-2 inhibitors. Lancet. 1999; 353(9162):1439-40.

414. Tustin T. COX-2 inhibitors. Lancet. 1999; 353(9162):1439.

415. Fruit and Vegetables for Health: Report of a Joint FAO / WHO Workshop. Joint FAO / WHO Workshop on Fruit and Vegetables for Health, 1-3 September 2004; Kobe, Japan.

416. NHS choices. Vitamins and minerals - vitamin A. Available from: www.nhs.uk/Conditions/vitamins-minerals/Pages/Vitamin-A.aspx.

417. NHS choices. Vitamins and minerals - vitamin C. Available from: www.nhs.uk/Conditions/vitamins-minerals/Pages/Vitamin-C.aspx.

418. NHS choices. Vitamins and minerals - vitamin E. Available from: www.nhs.uk/Conditions/vitamins-minerals/Pages/Vitamin-E.aspx.

419. Tunstall-Pedoe H. Cardiovascular Risk and Risk Scores: ASSIGN, Framingham, QRISK and others: how to choose. Heart. 2011; 97(6):442-4.

420. Wood D, Wray R, Poulter N, Williams B, Kirby M, Patel V, et al. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart. 2005; 91(SUPPL5): vi-v52).

421. Tunstall-Pedoe H, Woodward M, Watt G. ASSIGN, QRISK, and validation. British Medical Journal. 2009;339:b3514.

422. Arthritis Research UK. Diet and arthritis. Available from: http://www.arthritisresearchuk.org/arthritis-information/arthritis-and-daily-life/diet-and-arthritis.aspx.

423. Arthritis Care. Eating well. Available from: http://www.arthritiscare.org.uk/LivingwithArthritis/Self-management/Eatingwell

424. Perry ME, Burke JM, Friel L, Field M. Can training in musculoskeletal examination skills be effectively delivered by undergraduate students as part of the standard curriculum? Rheumatology. 2010; 49(9):1756-61.

425. Duruoz MT, Poiraudeau S, Fermanian J, Menkes CJ, Amor B, Dougados M, et al. Development and validation of a rheumatoid hand functional disability scale that assesses functional handicap. Journal of Rheumatology. 1996; 23(7):1167-72.

RELATED PUBLICATIONS

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EXTENDED REPORT

A pilot study of a Mediterranean-type diet intervention in female patients with rheumatoid arthritis living in areas of social deprivation in Glasgow

G McKellar, E Morrison, A McEntegart, R Hampson, A Tierney, G Mackle, J Scoular, J A Scott, H A Capell

Ann Rheum Dis 2007;**66**:1239–1243. doi: 10.1136/ard.2006.065151

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Background: A Mediterranean-type diet rich in fish, fruit and vegetables and low in saturated fats has been associated with health benefits, including improved cardiovascular profile and benefit in RA.
Objective: To overcome obstacles to healthy eating by a community-based intervention promoting a Mediterranean-type diet in patients with RA living in socially deprived areas of Glasgow.
Methods: 130 female patients with RA aged 30–70 years (median 55), disease duration 8 years were recruited from three hospital sites. The intervention group (n = 75) attended weekly 2-hour sessions for 6 weeks in the local community, including hands-on cooking classes backed up with written information. The control group (n = 55) were given dietary written information only. Both groups completed food frequency questionnaires (FFQs), and clinical and laboratory measures were assessed at baseline, 3 and 6 months.
Results: Significant benefit was shown in the intervention group compared with controls for patient global assessment at 6 months (p = 0.002), pain score at 3 and 6 months (p = 0.011 and 0.049), early morning stiffness at 6 months (p = 0.041) and Health Assessment Questionnaire score at 3 months (p = 0.03). Analysis of the FFQs showed significant increases in weekly total fruit, vegetable and legume consumption and improvement in the ratio of monounsaturated:saturated fat intake and systolic BP in the intervention group only. The cooking classes were positively received by patients and tutors; cost/patient for the 6 week course was £84 (€124).
Conclusions: Results demonstrate that a 6 week intervention can improve consumption of healthier foods. If implemented more widely it may prove a popular, inexpensive and useful adjunct to other RA treatment.

In the 1950s, the cook and writer Elizabeth David introduced *A Book of Mediterranean Food*[1] to a postwar Britain still under food rationing and so started our enthusiasm for this delicious cuisine. More recently, the health benefits of the Mediterranean diet have emerged. Characteristically this type of diet includes a high intake of fruit, vegetables, legumes, a moderate to high intake of fish, a low intake of dairy products and red meat and a high intake of unsaturated fats (especially olive oil) complemented by a modest amount of alcohol (mainly in the form of wine).

A Mediterranean diet has been associated with increased survival in older people in a large, prospective cohort study involving nine European countries[2] and has proved an effective intervention in both the primary[3] and secondary[4] prevention of coronary heart disease. An improved cardiovascular risk profile is probably mediated through a number of factors, including modification of hyperlipidaemia, hypertension and obesity as well as reduction in C reactive protein.[5] This last effect is potentially important in arthritis. A prospective, nested, case–control study[6] identified a high level of red meat consumption as a dietary risk factor for the development of inflammatory polyarthritis, while a similar study[7] noted that patients with a low intake of fruit and vitamin C (exogenous antioxidants) were more likely to develop arthropathy than matched controls. The precise mechanism of this effect is uncertain; these factors may be acting as markers in a group of people at increased risk from other, possibly lifestyle-related, factors. Indeed a recent cross-sectional study has shown that wine buyers purchase more healthy food items than people who buy beer.[8]

A 12 week randomised trial of Mediterranean diet intervention in 51 patients with RA demonstrated positive benefits, with a reduction in disease activity (measured by the 28 joint count Disease Activity Score (DAS28)), an improvement in physical function (Health Assessment Questionnaire (HAQ)) and increased vitality,[9] effects likely to be multifactorial. Further analysis showed an increase in reported consumption of antioxidant-rich foods during the Mediterranean diet intervention.[10] Intriguingly, the discovery of ibuprofen-like activity in extra-virgin olive oil may help to explain its effect.[11]

It is not clear, however, whether a Mediterranean-type diet could achieve similar results in patients with RA in a true-to-life setting, particularly in a population with high levels of social deprivation such as Glasgow, the largest city in Scotland. Any intervention requiring a change in lifestyle or behaviour, especially those which may be life long and culturally driven, is difficult to achieve and sustain. However, behavioural counselling to increase consumption of fruit and vegetables in lower income adults in the general population has led to sustained increases in intake.[12]

The gain from a Mediterranean-type diet intervention in patients with RA is potentially twofold. Firstly, improvement in disease activity and secondly, reduction in cardiovascular risk—people with RA are known to be at increased cardiovascular risk[13–15] and have increased cardiovascular disease mortality.[16] Social deprivation has an additional negative impact on both RA[17] and cardiovascular risk.[18]

Abbreviations: DAS28, 28 joint count Disease Activity Score; DMARD, disease modifying antirheumatic drug; EMS, early morning stiffness; FFQ, food frequency questionnaire; GGHBHPD, Greater Glasgow Health Board's Health Promotion Department; HAQ, Health Assessment Questionnaire; IL6, interleukin 6

Table 1 Group demographics at baseline

	Intervention (n = 75)			Control (n = 55)		
Demographics	Median	Mean	Interquartile range	Median	Mean	Interquartile range
Age (years)	58	55	47–64	52	53	45–61
Disease duration (years)	7	9.3	3.5–14	7	9.6	4–12
BMI (kg/m^2)	25.86	26.75	22–33	27.65	27.95	24–31

BMI, body mass index.

In this study we wished to explore the feasibility of introducing a Mediterranean-type diet to our female patients with RA living in areas of social deprivation and to assess change, if any, in lifestyle, disease activity and cardiovascular risk.

METHODS

One hundred and thirty female patients with RA aged 30–70 years were recruited over 9 months from three hospital sites—we aimed at recruiting residents from within any of the Social Inclusion Partnership areas in Glasgow, which are areas of social deprivation.

Intervention group

Patients in the intervention group (n = 75) attended a 6 week cookery course (with emphasis on a Mediterranean-type diet) organised by Greater Glasgow Health Board's Health Promotion Department (GGHBHPD) and delivered by nutritionists and teaching staff from local colleges. Occupational therapy staff advised about provision of aids for food preparation. The patients attended a weekly 2 hour cookery class, with a maximum of 10 participants in each session. Participants received a folder with written information on a Mediterranean-type diet, healthy eating and recipes which promoted the increased consumption of fruits, vegetables and legumes, along with the substitution of saturated fat with monounsaturated fat in the form of olive oil or spreads containing olive oil. In addition to ''hands-on'' food preparation, cooking and tasting, the participants received information about food hygiene, nutrition and local accessibility of affordable ingredients.

Control group

Control patients (n = 55) received readily available written information on healthy eating only.

Allocation

We originally intended to allocate patients randomly to intervention and control groups. However, a limiting factor proved to be the availability of a cookery course in a venue close to the patient's home at a time suitable to them. A more pragmatic approach was necessary, resulting in those able to attend on certain dates being allocated to the intervention group and those unavailable on dates of programmed courses becoming the control group.

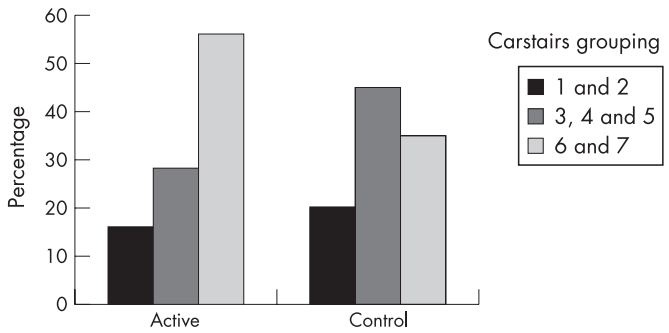

Figure 1 Influence of deprivation.

Patient assessment

Patients in both groups were assessed at baseline, 3 and 6 months.

Clinical features

Tender and swollen joint count, patient global pain score, duration of early morning stiffness (EMS), DAS28, HAQ score, erythrocyte sedimentation rate, C reactive protein, and interleukin 6 (IL6) were measured. IL6 is a proinflammatory cytokine and acts as a mediator in the acute phase response (higher levels of IL6 are present in more active disease).

Cardiovascular risk

Assessment included documentation of smoking habits, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol, glutathione and body mass index. Glutathione has important roles in preventing oxidative stress, metabolising nutrients and regulating cellular events. A deficiency of glutathione contributes to oxidative stress and can be implicated in the pathogenesis of heart disease.

Dietary assessment

Dietary data were collected using a previously validated food frequency questionnaire (FFQ),[19] which was completed by participants at the clinical assessment visits. The Mediterranean diet is rich in fruits, vegetables and legumes, which are good sources of the antioxidant vitamins A, C and E. If the intervention were successful in promoting dietary change, we would expect to see increases in intake of these food groups as well as the associated nutrients. A composite score of the weekly total number of servings of the three food groups was calculated. Additional questions about fruit intake were included in the FFQ as the DietQ FFQ collects only limited data on fruit consumption. These questions were analysed separately using the diet 5 computer package, and the nutrient data added to the data estimated by DietQ to calculate the daily intake of vitamins A, C and E.

Deprivation

The Carstairs grouping for each patient was noted[20] (derived from postcode, based on male employment, overcrowding, car ownership and social class).

Statistical analysis

A Wilcoxon matched-pairs signed-ranks test was used for within-group analyses and a Mann–Whitney U test for comparison between intervention and control groups.

Ethics

Local ethics committee approval was given before staring this study.

Table 2 Food frequency diaries at baseline and 3 months in the two groups

	Intervention (n = 75)			Control (n = 55)		
	0	3 Months	p Value	0	3 Months	p Value
Fruit, vegetables and legumes (portions/week)	23.5	26	**0.016**	21.5	23	0.84
Monounsaturated fats:saturated fats	0.86	0.92	**0.022**	0.82	0.83	0.726
Vitamin A (μg/day)	1108	1246	0.101	922	974	0.403
Vitamin C (mg/day)	94	104	0.081	94	94	0.929
Vitamin E (mg/day)	7.0	6.8	0.626	5.8	5.5	0.448

Results are shown as medians.

RESULTS

Table 1 shows that age, disease duration and body mass index were similar in both intervention and control groups.

As expected by the design of the study, the patients in the intervention group were more likely to be in the most deprived social classes 6 and 7, living in a Social Inclusion Partnership area (fig 1). Baseline cardiovascular risk based on blood pressure, age and smoking status was calculated for all patients using readily available and validated graphs[21]; none of the recruited patients had diabetes mellitus. Sixty per cent had a calculated cardiovascular disease risk of <10% over the next 10 years, 30% a risk of 10–20% and 10% a >20% risk.

Consumption of fruit, vegetables and legumes was below the recommended minimum of five portions a day, in both groups at baseline. By 3 months this had improved significantly in the intervention group who were attending cooking classes (table 2).

At the same time, this group also had a significant improvement in the ratio of monounsaturated:saturated fats consumed. Alcohol consumption was low in both groups with a mean consumption of 1.5 units/week in the intervention group and 1.9 units/week in the control group. We reviewed disease modifying antirheumatic drug (DMARD) treatment, examining any escalation of dose or addition of extra DMARD over the study period. Within the 6 months, 21.3% of the intervention group and 23.6% of the control group had such a change in their treatment.

Clinical assessments showed a significant benefit in the intervention group compared with the control group for patient global assessment at 6 months ($p = 0.002$), pain score at 3 and 6 months ($p = 0.011$ and 0.049), EMS at 6 months ($p = 0.041$) and HAQ at 3 months ($p = 0.03$)—Mann–Whitney calculations (table 3).

Evaluation of cardiovascular risk factors showed a significant drop in systolic blood pressure by an average of 4 mm Hg in the intervention group ($p = 0.016$), while the control group showed no change. No significant change in cholesterol or glutathione levels was found with this intervention (table 4).

The cost per patient for the 6 week cookery course was £84 (€124) (met by the GGHBHPD).

DISCUSSION

In this study we sought to assess whether we could modify dietary lifestyle, disease activity and cardiovascular risk in female patients with RA living in areas of social deprivation by introducing them to a Mediterranean-type diet. Cookery classes to provide ''hands-on'' experience of a Mediterranean-type diet were an essential element in increasing knowledge and confidence in the participants.

This study shows that this intervention was achievable and well received by patients. Intake of fruit, vegetables and legumes increased significantly over 3 months in the intervention group and the use of monounsaturated compared with saturated fats improved. The majority of the participants felt that the recipes were straightforward to make and affordable. Only three stated they were unable to purchase the necessary ingredients, either because they were too costly or were unavailable in their local shops. There were also wider social benefits in that most felt they had learnt new skills in food use and preparation. Some women also noted an improvement in confidence and self-esteem as they were now able to contribute more to cooking for themselves and their families at home.

We failed to see a significant improvement in the intake of the antioxidant vitamins A, C and E. Possibly, the FFQ was not sufficiently sensitive to detect changes in the actual nutrient intake. The FFQ was originally developed to assess the intake of total energy and macronutrients—protein, fat and carbohydrate—at a time when antioxidants were not the focus of interest.[19] The number of fruits and vegetables represented in the FFQ is relatively limited and it is possible that participants increased their intake with items not listed on the FFQ. A more accurate assessment of nutrient intake might have been

Table 3 Baseline Disease Activity Scores (DAS) and clinical outcomes at baseline, 3 and 6 months

	Intervention (n = 75)			Control (n = 55)			Mann–Whitney between groups
	0	3 Months	6 Months	0	3 Months	6 Months	
Tender joint count (0–28)	5	5	4	6	6	6	–
Swollen joint count (0–28)	6	5	4	6	5	5	–
Patient global VAS (0–100 mm)	50	50	45	54	55	63	6 Months **0.002**
Pain score VAS (0–100 mm)	50	50	50	55	62	63	3 Months **0.011** 6 Months **0.049**
EMS (min)	30	30	15	60	30	30	6 Months **0.041**
HAQ score (0–3)	1.75	1.625	1.625	1.75	1.875	1.875	3 Months **0.03**
DAS28	4.7	4.5	4.4	5.0	4.7	4.8	–
ESR (mm/1st h)	19	20	16	19	19	16	–
CRP (mg/l)	10	10	10	8.5	8	8	–
IL6 (pg/ml)	4.7	3.85	3.35	4.1	3.8	5.3	NS

Results are shown as medians.
VAS, visual analogue scale; EMS, early morning stiffness; HAQ, Health Assessment Questionnaire; DAS28, 28 joint count Disease Activity Score; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; IL6 interleukin 6; NS, not significant.

Table 4 Cardiovascular risk factors at baseline, 3 and 6 months

	Intervention (n = 75)				Control (n = 55)			
Risk factors	**0**	**3 Months**	**6 Months**	**Wilcoxon**	**0**	**3 Months**	**6 Months**	**Wilcoxon**
Ever smoker (%)	64				62			
Systolic BP (mm Hg)	132	130	128	**0.016**	130	129	130	NS
Diastolic BP (mm Hg)	80	78	80	NS	80	80	78	NS
Total cholesterol (mmol/l)	5.55	5.3	5.4	NS	5.3	5.18	5.4	NS
HDL (mmol/l)	1.55	1.6	1.6	NS	1.5	1.46	1.5	NS
TC:HDL ratio	3.44	3.40	3.40	NS	3.50	3.52	3.23	NS
Glutathione (nnmol/ml)	3.23	3.26	2.72	NS	2.94	3.2	2.66	NS
Weight (kg)	66.0	64.1	65.1	NS	70	70	72.5	NS
BMI (kg/m^2)	25.86	25	25.39	NS	27.65	27.65	28.22	NS

BP, blood pressure; TC, total cholesterol; HDL, high-density lipoprotein; BMI, body mass index; NS, not significant.

achieved by using 7-day weighed or estimated food diaries. However, this method places a heavy burden on the participant, which we did not think was appropriate given the age and health of our subjects. In addition, they are costly and time consuming to analyse: we did not have the funds to employ the specialist skills required to code and analyse food diaries.

We, like previous investigators,[9] have shown a modest improvement in a number of measures of disease activity. Pain score was significantly better in the Mediterranean diet group than in the controls at 3 and 6 months. Patient global assessment and reported EMS were significantly better at 6 months. Patient function, as assessed by the HAQ score, was also better in the intervention group at 3 months. Overall the DAS28 score remained unchanged in both groups, but despite this, patients in the intervention group clearly felt better. The reasons for this are likely to be multifactorial and may, in part, reflect increased confidence and self-esteem as well as dietary intervention. As it is impossible to conduct this type of study in a double-blind fashion, we cannot entirely exclude the possibility of a placebo response, but this seems less likely as the same trend was seen over a number of measurements and was sustained.

Patients with RA are at increased risk of cardiovascular events[13 14] and we also aimed to assess if we could modify this tendency in our patients. The intervention group lost weight (median 0.9 kg over the 6 month period), whereas the control group showed a weight gain (median 3 kg). However, this difference was not statistically significant. Cholesterol levels (at baseline and 6 months) and smoking status did not differ between the two groups. We noted a small (mean 4 mm Hg) but significant reduction in systolic blood pressure in the intervention group. This was not attributable to the prescription of, or changes to, anti-hypertensive treatment. However, the magnitude of the change noted is perhaps what we might achieve with the introduction of a mild anti-hypertensive agent in routine practice. The benefit to patients is that this was achieved without an addition to their drugs.

This study has shown that female patients with RA following a Mediterranean-type diet derive modest benefits across a range of areas, suggesting that this type of intervention may be a useful therapeutic adjunct to conventional DMARDs, feasible in routine clinical practice and popular with patients.

The initial objectives when designing this study were to assess if lifestyle, disease activity or cardiovascular risk might be altered by this type of intervention. The results show that this is indeed achievable at low cost and is acceptable to patients with RA.

To act on and implement these findings we have approached local and national (Scottish) public health authorities to inform them of the results and discuss the potential impact of assessment in a larger population.

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REFERENCES

1 **David E**. *A book of Mediterranean food*. London: Penguin, 1998.
2 **Trichopoulou A**, for members of the EPIC-Elderly Prospective Study Group. Modified Mediterranean diet and survival: EPIC-Elderly prospective cohort study. *BMJ* 2005;**330**:991–5.
3 **Trichopolou A**, Costacou T, Bamia C, Trichopolos D. Adherence to Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003;**348**:2599–608.
4 **De Lorgeril M**, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, *et al*. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;**343**:454–9.
5 **Ridker PM**, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;**342**:836–43.
6 **Pattison DJ**, Symmons DPM, Lunt M, Welch A, Luben R, Bingham SA, *et al*. Dietary risk factors for the development of inflammatory polyarthritis. Evidence for a role of high level of red meat consumption. *Arthritis Rheum* 2004;**50**:3804–12.
7 **Pattison DJ**, Silman AJ, Goodson NJ, Lunt M, Bunn D, Luben R, *et al*. Vitamin C and the risk of developing inflammatory polyarthritis: prospective nested case-control study. *Ann Rheum Dis* 2004;**63**:843–7.
8 **Johansen D**, Friis K, Skovenborg E, Grønbaek M. Food buying habits of people who buy wine or beer: cross-sectional study. *BMJ* 2006;**332**:19–21.
9 **Sköldstam L**, Hagfors L, Johansen G. An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. *Ann Rheum Dis* 2003;**62**:208–14.
10 **Hagfors L**, Leanderson P, Sköldstam L, Andersson J, Johansen G. Antioxidant intake, plasma antioxidants and oxidative stress in a randomised, controlled, parallel, Mediterranean dietary intervention study on patients with rheumatoid arthritis. *Nutr J*. 2003;2: 1–11, Available at http://www.nutritionj.com/content/2/1/5 (accessed 28 March 2007).
11 **Beauchamp GK**, Keast RSJ, Morel D, Lins J, Pikas J, Han Q, *et al*. Ibuprofen-like activity in extra-virgin olive oil. *Nature* 2005;**437**:45–6.
12 **Steptoe A**, Perkins-Porras L, McKay C, Rink E, Hilton S, Cappuccio FP. Behavioural counselling to increase consumption of fruit and vegetables in low income adults: randomised trial. *BMJ* 2003;**326**:855–8.
13 **McEntegart A**, Capell HA, Creran D, Rumley A, Woodward M, Lowe G. Cardiovascular risk factors, including thrombotic variables, in a population with rheumatoid arthritis. *Rheumatology (Oxford)*, 2001;**40**:640–4.

14 **Alkaabi JK**, Ho M, Levison R, Pullar T, Belch J. Rheumatoid arthritis and macrovascular disease. *Rheumatology (Oxford)*, 2003;**42**:292–7.
15 **Hall FC**, Dalbeth N. Disease modification and cardiovascular risk reduction: two sides of the same coin? *Rheumatology (Oxford)*, 2005;**44**:1473–82.
16 **Goodson N**, Marks J, Lunt M, Symmons D. Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. *Ann Rheum Dis* 2005;**64**:1595–601.
17 **McEntegart A**, Morrison E, Capell HA, Duncan MR, Porter D, Madhok R, *et al*. Effect of social deprivation on disease severity and outcome in patients with rheumatoid arthritis. *Ann Rheum Dis* 1997;**56**:410–13.
18 **Tunstall-Pedoe H**, Woodward M, for the SIGN group on risk estimation. By neglecting deprivation, cardiovascular risk scoring will exacerbate social gradients in disease. *Heart* 2005;**92**:307–10.
19 **Yarnell JWG**, Fehily AM, Milbank JE, Sweetname PM, Walker CL. A short dietary questionnaire for use in an epidemiological survey: comparison with weighed dietary records. *Hum Nutr Appl Nutr* 1983;**37A**:103–12.
20 **Carstairs V**, Morris R. *Deprivation and health in Scotland*. Aberdeen: Aberdeen University Press, 1991.
21 **Anonymous**. *British National Formulary*, 51st ed. London: Pharmaceutical Press, 2006.

Nonsteroidal Antiinflammatory Drug Withdrawal in Patients with Stable Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate the effect of nonsteroidal antiinflammatory drug (NSAID) withdrawal on blood pressure (BP), 44-joint Disease Activity Score (DAS44), and functional assessments in patients with stable rheumatoid arthritis (RA).

Methods. NSAID was withdrawn from 30 patients with stable RA (DAS44 ≤ 2.8). Other prescribed medication continued. Clinical and laboratory measures were taken at baseline, 6 weeks, and 12 weeks.

Results. No participants required NSAID reintroduction during the study period. Significant improvement in systolic BP was noted: maximal median reduction was 7 mm Hg (baseline to 12 weeks). There was no significant deterioration in DAS44 or function. Eleven participants required additional intervention.

Conclusion. NSAID withdrawal resulted in improvement in BP without loss of disease control.
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Key Indexing Terms:
BLOOD PRESSURE
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RHEUMATOID ARTHRITIS
RISK FACTORS

The morbidity and mortality associated with rheumatoid arthritis (RA) is well documented; life span is reduced by 3–18 years[1]. This excess mortality is due to cardiovascular (CV) events, secondary to atheromatous vascular disease. Inflammatory mechanisms are a key response in the initial endothelial damage and the subsequent progression of atheromatous plaques. General population estimates calculate that > 70% of those with atheroma-related CV disease have ≥ 1 traditional Framingham risk factor[2].

Nonsteroidal antiinflammatory drugs (NSAID) are frequently prescribed to patients with RA. Most of these drugs raise blood pressure (BP) by about 5 mm Hg[3]. Accumulating evidence has implicated cyclooxygenase-2-specific and nonselective NSAID with an increase in acute myocardial infarctions[4,5]. In 2006, the American Heart Association advised that to minimize CV risk, anyone prescribed an NSAID should have the lowest dose administered for the shortest possible time[6].

Although clinical experience and expert opinion advise that NSAID should be withdrawn in patients with RA who have well controlled disease[7], there is no evidence that this improves the risk/benefit ratio associated with their use. Our aim with this study was to evaluate the feasibility of NSAID withdrawal and to identify potential benefits from withdrawal in patients with stable RA, focusing on disease activity and BP control.

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MATERIALS AND METHODS

Local ethics committee approval was given. Study enrollment is documented in Figure 1 and inclusion and exclusion criteria in Table 1. Thirty patients were recruited and gave written informed consent. As this was an open-label observational feasibility study, no specific power calculations were performed. A sample size of 30 patients was considered large enough to provide helpful results but small enough to allow rapid followup.

Patients were asked to stop prescribed NSAID abruptly, without tapering the dose. Disease-modifying antirheumatic drug (DMARD) therapy was continued. General practitioners were asked not to prescribe NSAID for the duration of our study and patients were requested not to self-administer over-the-counter NSAID, as explained in the patient information sheet. Use of acetaminophen or codeine-containing compound analgesia was allowed. Patients were encouraged to make telephone contact if further advice was required between scheduled visits. If appropriate, steroid injection or dose escalation of DMARD could be arranged (as per study regimen).

These clinical features were documented at baseline, 6 weeks, and 12 weeks: tender and swollen joint count, erythrocyte sedimentation rate, patient global assessment of disease activity (visual analog scale, VAS), DAS44, pain score (VAS), and Short Form-12 v2 Health Survey (SF-12) functional assessment[8].

These CV risk factors were documented: smoking habits, systolic and diastolic BP, total and high-density lipoprotein cholesterol, triglycerides, and body mass index (BMI). A British Hypertension Society (BHS)-approved digital sphygmomanometer was used throughout the study to record BP. BHS guidelines were followed for BP recordings[9].

SPSS version 15.0 software was used for statistical analysis.

RESULTS

Baseline demographic and clinical characteristics are documented in Table 2. Forty-seven percent of participants were

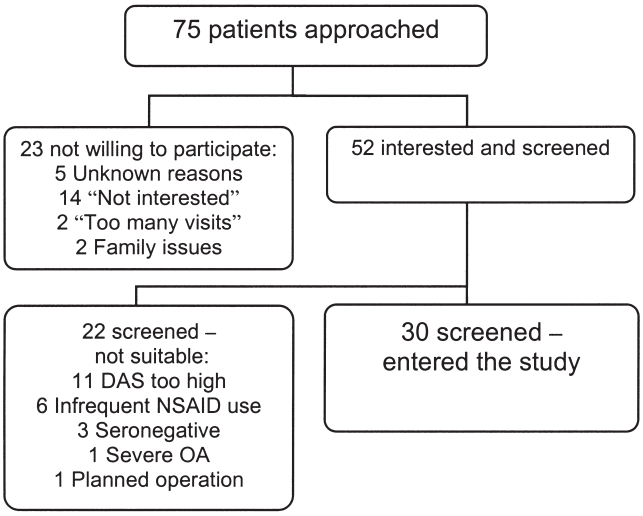

Figure 1. Selection of participants for the study. DAS: Disease Activity Score; NSAID: nonsteroidal antiinflammatory drug; OA: osteoarthritis.

Table 1. Study inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Rheumatoid factor seropositivity	Concurrent diagnoses of
DAS44 ≤ 2.8	Fibromyalgia
Stable dose DMARD for ≥ 1 month	Severe osteoarthritis
Prednisolone ≤ 10 mg/day (if taken)	Dysmenorrhea
NSAID used on ≥ 25/30 days per month	Planned operative intervention

DAS44: 44-joint Disease Activity Score; DMARD: disease-modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug.

ever-smokers and 20% were current smokers. One-third were classified as obese (BMI > 30 kg/m^2). One patient was prescribed low-dose prednisolone and 3 patients antitumor necrosis factor therapy at study outset. All 30 patients completed the 12-week study without reintroduction of NSAID.

A significant reduction in systolic BP was observed with NSAID withdrawal at Week 6 (median reduction of 5 mm Hg; p = 0.025) and Week 12 (median reduction 7 mm Hg compared with baseline; p = 0.037; Table 2). No significant change in diastolic BP was recorded. Of the patients prescribed antihypertensives (40%), none had their regimen altered during the intervention period. Changes in systolic BP over the course of study participation for each patient are documented in Figure 2.

There was no overall change in DAS44. A significant increase was seen in patient global assessment and pain score from baseline to 6 weeks (p = 0.009 and p < 0.0001, respectively), but there was a significant reduction in both measures back to near baseline values by 12 weeks. At baseline, the median SF-12 physical score was < 50, representing a below-average physical function. There was a nonsignificant trend in reduction in physical component score from baseline to 6 weeks. By 12 weeks there was a significant improvement in this measure.

A total of 13 steroid injections were given to 11 study participants over the entire intervention period. Only 1 participant required increased DMARD dose.

DISCUSSION

We have demonstrated that NSAID withdrawal is feasible in this group, with minimal additional intervention. No significant deterioration was noted in self-assessed function, as measured by SF-12.

Hypertension is one of the most important Framingham risk factors contributing to overall CV risk. It was therefore relevant that we found NSAID withdrawal resulted in a median 7 mm Hg fall in systolic BP at 12 weeks compared to baseline. A 3 mm Hg rise in systolic BP increases the occurrence of congestive cardiac failure by 10%–20%, the risk of stroke by 15%–20%, and angina by 12%[10]. A larger randomized controlled study may go some way to explain the cause of the improved BP, which at the moment remains hypothetical. One possibility is that the patients may have become acquainted with and relaxed within the study environment, with reduction in BP ensuing. We do not know whether BP changes are limited to certain levels. The early increase in pain and patient global scores may have been minimized by a tapered dose reduction of NSAID.

We acknowledge the limitations of our open-label, nonrandomized study, with small numbers and short duration. Data regarding steroid injection requirements pre-NSAID withdrawal may have aided comparison. Ours was a preliminary study intended to inform future work. We proposed to study patients with RA with a low to moderate DAS, but the local ethics committee advocated restricting the study to patients with low DAS. This is to our knowledge the first supportive evidence to guide the limitation of NSAID use in stable RA. We demonstrate that it is possible to withdraw NSAID in patients with a low DAS without adversely affecting their quality of life or disease control and without the need for significant additional input. We have also demonstrated additional benefits on systolic BP control that has important implications for reducing CV risk. Future studies of CV risk in RA should take into account the influence of NSAID-induced hypertension.

ACKNOWLEDGMENT

We acknowledge the input and support of Prof. Iain McInnes.

REFERENCES

1. Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, et al. The mortality of rheumatoid arthritis. Arthritis Rheum 1994;37:481-94.
2. Wilson PW. Established risk factors and coronary artery disease: the Framingham Study. Am J Hypertens 1994;7 part 2:7S-12S.
3. Johnson AG, Nguyen TV, Day RO. Do non-steroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994;121:289-300.

Table 2. Demographic and clinical variables at baseline, 6 weeks, and 12 weeks. Data are median (range) unless otherwise specified.

Variables	Baseline	Week 6	Week 12
Age, yrs	59 (33–73)	—	—
Disease duration, yrs	11 (1–40)	—	—
Female sex, %	73	—	—
Total cholesterol, mmol/l	5.15 (3.4–7.4)	—	—
High-density lipoprotein, mmol/l	1.4 (0.8–32)	—	—
Triglycerides, mmol/l	1.05 (0.5–3.6)	—	—
Body mass index, kg/m^2	26.6 (22.04–44.74)	—	—
Systolic BP, mm Hg	141 (109–190)	136* (104–170)	134** (106–171)
Diastolic BP, mm Hg	87 (72–103)	85 (66–99)	84 (72–105)
DAS44	2.08 (0.26–2.79)	2.19 (0.65–5.08)	1.79 (0.76–2.95)
ESR, mm/1st h	5 (2–35)	8 (2–51)	7 (2–38)
Patient global assessment, VAS 100 mm	29 (4–61)	43*** (7–77)	25† (1–55)
Pain score, VAS 100 mm	20 (4–53)	37†† (7–72)	25$^{\#}$ (1–72)
SF-12 physical component	37.4 (24.5–56.6)	34.4 (24.5–55.1)	40.3 (31.6–56.7)
SF-12 mental component	54.4 (30.4–66.5)	54.0 (27.1–63.4)	54.5 (38.4–66.1)

Compared with baseline data (Wilcoxon matched-pairs signed-rank test): * p = 0.025 (improvement); ** p = 0.037 (improvement); *** p = 0.009 (deterioration); †† p < 0.0001 (deterioration). Compared with 6-week data (Wilcoxon matched-pairs signed-rank test): † p = 0.003 (improvement); $^{\#}$ p = 0.008 (improvement). BP: blood pressure; DAS44: 44-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; VAS: visual analog scale; SF-12: Medical Outcomes Study Short Form-12 Health Survey.

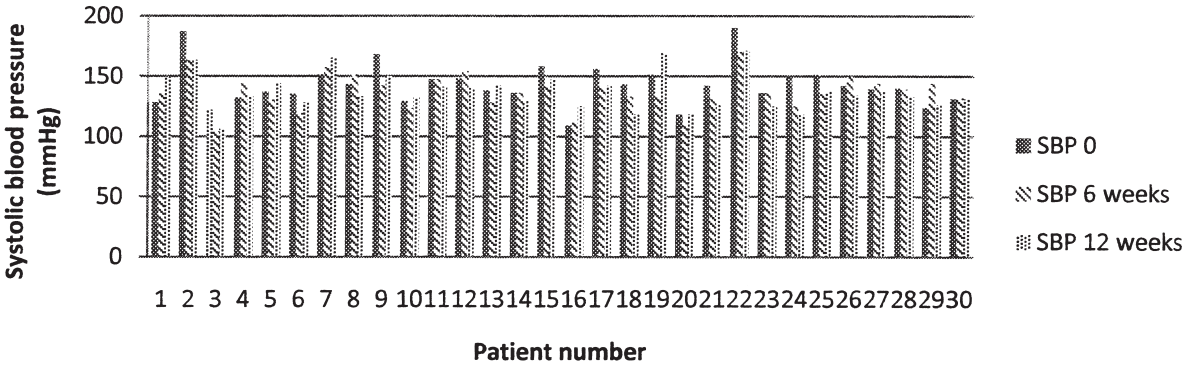

Figure 2. Systolic blood pressure (SBP) readings for individual patients at baseline, 6 weeks, and 12 weeks.

4. Singh G, Wu O, Langhorne P, Madhok R. Risk of acute myocardial infarction with non-selective non-steroidal anti-inflammatory drugs: a meta-analysis. Arthritis Res Ther 2006;8:R153.
5. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA 2006;296:1633-44.
6. Antman EM, Bennett JS, Daugherty A, Fuberg C, Roberts H, Taubert KA. Use of non-steroidal anti-inflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation 2007;115:1634-42.
7. Management of early rheumatoid arthritis. Scottish Intercollegiate Guidelines Network publication no. 123. [Internet. Accessed May 26, 2011.] Available from: http://www.sign.ac.uk/guidelines/fulltext/123/index.html
8. The SF-12 Health Survey. [Internet. Accessed May 26, 2011.] Available from: www.sf-36.org/tools/sf12.shtml
9. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, et al. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens 2003;21:821-48.
10. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomised to doxazosin vs chlorthalidone. JAMA 2000;283:1967-75.

The Problem with NSAIDs: What Data to Believe?

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Patients with rheumatoid arthritis and osteoarthritis have relied upon NSAIDs as a cornerstone of their analgesic regime for decades. The choice of anti-inflammatory agents broadened for this group of patients when the selective inhibitors of cyclooxygenase-2 enzyme were developed. Much has been published in the past few years regarding the superior gastrointestinal safety of this class of drugs when compared with traditional NSAIDs. Their triumphant debut was swiftly followed by the emergence of data detailing their associated increased serious cardiovascular risks. This also led to a reevaluation of data concerning more traditional NSAIDs, and surprisingly, a similar trend was seen. The US Food and Drug Administration has recommended that both classes of drugs carry a black box warning with regard to gastrointestinal and cardiovascular risks.

Introduction

The scale of the arthritides is huge: in the United States, rheumatoid arthritis (RA) affects around 2 million people; osteoarthritis affects around 20 million people [1]. Consequently, NSAIDs have become and remain one of the most commonly used classes of medication prescribed worldwide for pain and inflammation [2] and are frequently prescribed by rheumatologists and primary care physicians. Their gastrointestinal toxicity is now well-documented, and this evidence warrants further review. The introduction of selective cyclooxygenase-2 (COX2) inhibitors, such as rofecoxib and celecoxib, was heralded as a new dawn in anti-inflammatory therapy because of their superior gastrointestinal safety profile.

In September 2004, Merck and Company voluntarily withdrew rofecoxib because of an increased risk of myocardial infarction (MI) and stroke [3]. Soon after, the US Food and Drug Administration (FDA), in a public health advisory, placed strict limitations on the use of other NSAIDs, including celecoxib [4], and valdecoxib was withdrawn from the market. Subsequently, this has led to the review and identification of similar risk with a number of traditional NSAIDs. We review the recently published literature and discuss the evidence behind these risks.

NSAIDs

Scientific information

All NSAIDs reduce prostaglandin production and result in relief from hyperalgesia (increased sensitivity to pain) caused by tissue damage [5]. Individual compounds vary in their chemical structure and ability to block COX1 in preference to COX2. These drugs reach high concentrations in inflamed tissues, leading to inhibition of prostaglandin synthesis at the desired site of action; however, they also reach high concentrations in other organs and in the blood, leading to the side effects that can be experienced by patients [6].

Cardiovascular

Because the cardiovascular benefits of aspirin come from its inhibition of COX1, it seems sensible to think that NSAIDs would therefore not increase the risk of cardiovascular events. However, a near-complete inhibition of platelet COX1 is required for this cardioprotective benefit, something that a non-aspirin NSAID cannot accomplish in a sustained fashion. No placebo-controlled trial has ever studied the cardiovascular risk of non-selective NSAID therapy. However, it seems unlikely that such a trial would ever be funded in the current climate; it would be unethical to randomize patients to an intervention that may be potentially harmful.

Several meta-analyses have concluded from review of observational studies that the risk of MI varies between individual NSAIDs [7,8••,9••]. McGettigan and Henry [9••] reviewed 23 studies' databases and showed that diclofenac had a relative risk (RR) for MI of 1.4 (95% CI = 1.16–1.7), higher than other traditional NSAIDs.

A further meta-analysis, looking at both COX2 inhibitors and traditional NSAIDs [10], reviewed the specific comparison of NSAIDs with placebo in detail. Differences were again shown between individual preparations—naproxen was associated with the lowest risk (RR = 0.92, 95% CI = 0.67–1.21), and ibuprofen and diclofenac with the highest (RR = 1.51 [0.96–2.37] and 1.63 [1.12–2.37], respectively). The Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study [11••], discussed later in this paper in more detail, demonstrated similar rates of thrombotic cardiovascular events between etoricoxib and diclofenac.

Gislason et al. [12] reported on the risk of death or reinfarction associated with non-selective NSAIDs as well as selective COX2 inhibitors in patients discharged from a Danish hospital after an MI. A substantial risk was again confirmed with traditional therapies; ibuprofen or diclofenac were associated with a 1.5- to 2.4-fold increased risk of death. Again, a strong dose-response relationship was identified. With any observational study, such as this, unmeasured confounders cannot be accounted for. No information was given on concomitant use of aspirin in this study. Few of the studies that the meta-analyses were drawn from recorded the indication for or duration of NSAID use. Although the size of the overall patient risk appears small, the absolute risk may be considerable due to the large number of patients prescribed NSAIDs.

The adverse event of hypertension is common with NSAID and COX2 inhibitors. Most NSAIDs increase blood pressure by 3 to 5 mm Hg [13,14], and even such a modest rise can significantly increase the frequency of cardiovascular events, including ischemic heart disease and heart failure [15,16]. A nested case-control study of 1396 cases of first admission to hospital for heart failure showed an overall 30% increase in those prescribed NSAIDs, versus the control group [17]. The risk of hospitalization varied with different NSAIDS, with higher risks seen with indomethacin and naproxen, and in the presence of comorbidities such as hypertension and diabetes. The authors postulate that this equates to one extra case per year of first heart failure–related hospital admission for every 1000 NSAID users aged 60 to 84 years.

Gastrointestinal

The problem of oral NSAID therapy and associated gastrointestinal adverse effects is great and well-documented in the medical literature. Serious gastrointestinal complications occur in 1% to 4% of NSAID users per year [18–22]. A large retrospective review of nearly 3000 cases of upper gastrointestinal (UGI) bleeding in Spain has given valuable real-life information regarding this clinical problem [23]. Twenty-four percent of the patients with bleeding had taken a non-aspirin NSAID in the week before admission. Naproxen was the NSAID associated with the highest risk of bleeding (RR = 7.3, 95% CI = 4.7–11.4). The combination of NSAID plus low-dose aspirin increased this risk even further (RR = 12.7, 95% CI = 7–23). This study also identified that diclofenac and ibuprofen had the lowest risk profile of the traditional NSAIDs for UGI bleed. These data are corroborated in work data from Singh et al. [24]—multivariate adjusted rate ratios: ibuprofen = 1.57 (95% CI = 1.41–1.74, $P < 0.0001$), diclofenac = 1.72 (1.49–1.98, $P < 0.0001$), naproxen = 3.07 (2.74–3.44, $P < 0.0001$). Proton pump inhibitors have consistently been shown to be more effective than H_2-receptor antagonists and prostaglandin analogues in the prophylaxis and treatment of gastrointestinal damage in patients who require continuous NSAID therapy [25].

It is commonplace to prescribe a cardioprotective dose of aspirin to some patients; this, in addition to NSAID therapy, increases the risk of acute UGI bleed from an OR of 4 for aspirin alone (95% CI = 3.2–4.9) to 17.5 (11.9–25.8) [26]. The addition of a proton pump inhibitor to this combination reduces the OR to 1.1 (0.5–2.6). Therefore, careful consideration of adding a proton pump inhibitor should be given to all NSAID patients who are also prescribed aspirin. A Cochrane review supports the safety of this approach [27]. An additional potentially modifiable risk factor is any *Helicobacter pylori* infection; Chan et al. [28] have shown that in the short term, *H. pylori* eradication decreases the incidence of peptic ulcer disease in patients who begin NSAID therapy.

COX2 Inhibitors

Scientific information

The primary property of this class of drugs is the inhibition of the COX2 enzyme. Initial research postulated that COX1 was continuously expressed in most tissues, whereas COX2 was induced in inflammation. Recent evidence has shown that COX2 is constitutively expressed in several organs and systems, including the kidney, central nervous system, and vascular wall [29], and that it can adversely influence the prostacyclin:thromboxane (anti-thrombotic: prothrombotic) ratio in the vascular wall [30]. This may then promote platelet aggregation and atherosclerosis, resulting in an increased burden of cardiovascular toxicity.

Cardiovascular

In 2000, an early study of major gastrointestinal events showed an unexpected fivefold increase in the risk of acute MI with rofecoxib, compared with naproxen. At the time of publication, many hypothesized that this was due to the cardioprotective effect of naproxen, rather than prothrombotic side effects of rofecoxib [31]. However, in September 2004, rofecoxib was eventually withdrawn from worldwide sale based on the safety findings of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study [32]. In this study, long-term use of rofecoxib, 25 mg daily, showed a 3.5% incidence of

MI or ischemic stroke when compared with placebo in patients with no pre-existing history of cardiovascular disease (1.9% of placebo group, $P < 0.001$). A few months later, the Adenoma Prevention with Celecoxib (APC) study group [33] published an interim analysis of their data, which showed that celecoxib at supra-therapeutic doses was also associated with an increased risk of cardiovascular thrombotic events. Promptly thereafter, the National Institutes of Health halted a trial involving research of COX2 inhibitors in Alzheimer's disease because of their cardiovascular safety. The FDA, European Agency for the Evaluation of Medicinal Products, and the Medicines and Healthcare Products Regulatory Agency have all issued recommendations that COX2 inhibitors should not be prescribed for those with pre-existing ischemic heart disease or cerebrovascular disease [34–36].

Kearney et al. [10] have undertaken a meta-analysis of data of vascular events from randomized controlled trials of COX2 inhibitors. In all studies, COX2 inhibitors increased the risk of vascular events, mainly acute MI, by 42% (RR = 1.42, 95% CI = 1.13–1.78). Studies that compared a COX2 inhibitor with a traditional NSAID (91 trials) showed no significant difference in the risk of vascular events (RR = 1.16, 95% CI = 0.97–1.38). In a similar meta-analysis, McGettigan and Henry [9••] reviewed 23 studies' databases and confirmed the dose-related increased risk with rofecoxib (≤ 25 mg/day: RR = 1.33, 95% CI = 1–1.79; ≥ 25 mg/day: RR = 2.19, 1.64–2.91).

It is worth interrogating the data of the MEDAL program in more detail, in which the authors set out to assess the relative cardiovascular toxicity of diclofenac and etoricoxib in patients with RA aged older than 50 years [11••]. Patients with cardiovascular and gastrointestinal risk factors were included in order to assess the widest possible range of comorbidities. Data were pooled from three separate pharmaceutical industry–sponsored randomized double-blind clinical trials, totaling approximately 25,000 osteoarthritis and 10,000 RA patients. Nearly 17,000 patients received etoricoxib, and slightly fewer received diclofenac. The numbers of thrombotic cardiovascular events were similar in both groups, with higher risks of UGI events in the diclofenac group (0.97 per 100 patient-years). The lack of placebo group limits the ability to ascertain the absolute cardiovascular risks of the two drugs. The MEDAL data vary from the results of the nested case control study by Andersohn et al. [37], in which etoricoxib was associated with an RR of 2.09 for acute MI (95% CI = 1.1–3.97) and diclofenac with an RR of 1.37 (1.17–1.59).

Cerebrovascular

Until 2006, there had been few data published regarding the risk of ischemic stroke with COX2 inhibitors. A large case-control study [38] found that current use of rofecoxib and etoricoxib was associated with a significantly increased risk of ischemic stroke (multivariate OR = 1.71 and 2.38, respectively); the risk was maintained even if the patient had no pre-existing history of cerebrovascular disease, hypertension, or atrial fibrillation. Singh et al. [39] presented data this year from a nested case-control study reviewing the risk of stroke with COX2 inhibitor and NSAID therapy in patients with arthritis. This showed the highest risk was with rofecoxib (multivariate-adjusted stroke rate ratio = 1.26 [95% CI = 1.17–1.36; $P < 0.0001$]) and valdecoxib (RR = 1.22, 1–1.5, $P < 0.05$). The NSAIDs, including celecoxib, which exert less effect on blood pressure, did not increase the risk of stroke (RR = 0.97, 0.91–1.05).

Gastrointestinal

One advantage of COX2 inhibitors over NSAIDs is a better gastrointestinal safety profile, and this attractive selling point was at the crux of initial marketing of this class of drug, on the basis of two large gastrointestinal outcome studies [31,40]. The Successive Celecoxib Efficacy and Safety Study I (SUCCESS-I), a large multinational, randomized, double-blind, controlled trial, compared the UGI safety of celecoxib with naproxen and diclofenac in a cohort of more than 13,000 patients with osteoarthritis [41]. Of the randomized celecoxib group, 37.2% had gastrointestinal symptoms, compared with 40.3% in the NSAID group ($P < 0.001$), with an OR for complicated UGI side effects of 6.02 (95% CI = 1.5–34.57) in the NSAID group. Encouragingly, celecoxib was found to be as effective as traditional NSAIDs in efficacy for treating osteoarthritis symptoms. The SUCCESS-I study is the first such large trial to conclusively establish the gastrointestinal safety profile of celecoxib; other large outcome studies had shown no difference in complicated UGI events between etoricoxib and diclofenac [42].

The initial study of COX2 inhibitors for prevention of adenomatous polyps first brought their potential cardiovascular effects into the public domain. These studies included APPROVe [32], APC [33,43], and Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) [44]. Although they showed a reduction in the rate of adenoma formation, the documented associated increased rate of cardiovascular events caused their withdrawal from the market, and this avenue of chemoprevention was not further pursued.

It is important to pay close attention to the comparator NSAID in studies showing a gastrointestinal safety advantage of COX2 inhibitors because traditional NSAIDs vary in their risk of serious gastrointestinal side effects [24]. "Gastrointestinal toxic" NSAIDs such as naproxen are more likely to show a statistical advantage over COX2 inhibitors, as in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study [31]. This is in comparison with less "toxic" NSAIDs, such as diclofenac (used in the MEDAL study [11••]). Head-to-head clinical trials may be required to highlight any

differences between the gastrointestinal safety profiles of individual COX2 inhibitors.

Conclusions

There is considerable evidence to suggest that the gastrointestinal toxicity profiles of NSAIDs vary widely—naproxen has a consistently high gastrointestinal toxicity, whereas diclofenac and ibuprofen are less injurious to the gastrointestinal tract. Thus, it is imperative to consider the comparator NSAID when evaluating the gastrointestinal toxicity of any new COX2 inhibitor preparation.

Both nonselective NSAIDs and COX2 inhibitors effectively reduce joint pain and inflammation. Gastrointestinal risk factors for each patient need to be identified and used in treatment decisions because both carry a gastrointestinal hazard (albeit lesser in the COX2 inhibitor group).

In this complex milieu, physicians need to balance each patient's personal gastrointestinal and cardiovascular risks, the potential benefit of treatment, and ultimately, the cost effectiveness of such a strategy. Patients with gastrointestinal risk and no cardiovascular risk may benefit from a nonselective traditional NSAID with gastroprotection. Those with gastrointestinal and cardiovascular risk who require the prescription of aspirin also require gastroprotection with whichever anti-inflammatory is used, but perhaps a better option may be a short course of lowest-dose NSAID [45]. By considering all of the factors involved and the well-judged use of NSAIDs and gastroprotection, patients can still receive treatment that gives them the most benefit while minimizing their individual risk profile.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Lawrence RC, Helmick CG, Arnett FC, et al.: **Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States.** *Arthritis Rheum* 1998, **41:**778–799.
2. Singh G: **Treatment options for osteoarthritis.** *Surg Technol Int* 2003, **11:**287–292
3. Krumholz HM, Ross JS, Presler AH, Egilman DS: **What have we learnt from Vioxx?** *Br Med J* 2007, **334:**120–123.
4. US food and Drug Administration: **Public health advisory: non-steroidal anti-inflammatory drug products (NSAIDs). December 23, 2004.** Available at http://www.fda.gov/cder/drug/advisory/nsaids.htm. Accessed July 2006.
5. Brune K, Zeilhofer HU: **Antipyretic analgesics: basic aspects.** In *Textbook of Pain,* edn 5. Edited by McMahon SB, Koltzenburg M. Philadelphia: Elsevier; 2005:459–470.
6. Vane J, Botting R: **Inflammation and the mechanism of action of anti-inflammatory drugs.** *FASEB J* 1987, **1:**89–96.
7. Hernandez-Diaz S, Varas-Lorenzo C, Garcia Rodriguez LA: **Non-steroidal anti-inflammatory drugs and the risk of acute myocardial infarction.** *Basic Clin Pharmacol Toxicol* 2006, **98:**266–274.
8. •• Singh G, Wu O, Langhorne P, Madhok R: **Risk of acute myocardial infarction with nonselective non-steroidal anti-inflammatory drugs: a meta-analysis.** *Arthritis Res Ther* 2006, **8:**R153

A meta-analysis of 14 large studies that confirms an increased risk of acute MI with non-selective NSAIDs, with variation between several individual preparations. Diclofenac and ibuprofen had the highest risk.

9. •• McGettigan P, Henry D: **Cardiovascular risk of inhibition of cyclo-oxygenase.** *JAMA* 2006, **296:**1633–1644.

Large meta-analysis that reviews data from 17 case-control and six cohort studies; an increased risk was seen with diclofenac and a dose-related increase with rofecoxib.

10. Kearney PM, Baignent C, Godwin J, et al.: **Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials.** *Br Med J* 2006, **332:**1302–1308.
11. •• Cannon CP, Curtis SP, FitzGerald GA, et al.: **Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison.** *Lancet* 2006, **368:**1771–1781.

A large cohort of patients, pooled from three separate randomized, double-blinded trials. Outcomes showed similar rates of thrombotic cardiovascular events with diclofenac and etoricoxib.

12. Gislason GH, Jacobsen S, Rasmussen JN, et al.: **Risk of death or reinfarction associated with the use of selective cyclooygenase-2 inhibitors and non-selective non-steroidal anti-inflammatory drugs after acute myocardial infarction.** *Circulation* 2006, **113:**2906–2913.
13. Aisen PS, Schafer K, Grundman M et al.: **NSAIDS and hypertension.** *Arch Intern Med* 2003, **163:**1115.
14. Johnson AG, Nguyen TV, Day RO: **Do non-steroidal anti-inflammatory drugs affect blood pressure? A meta-analysis.** *Ann Intern Med* 1994, **121:**289–300.
15. Singh G, Miller JD, Huse DM, et al.: **Consequences of increased systolic blood pressure in patients with osteoarthritis and rheumatoid arthritis.** *J Rheumatol* 2003, **30:**714–719.
16. ALLHAT Collaborative Research Group: **Major cardiovascular events in hypertensive patients randomised to doxazosin vs chlorthalidone.** *JAMA* 2000, **283:**1967–1975.
17. Huerta C, Varas-Lorenzo C, Castellsague J, Garcia Rodriguez LA: **Non-steroidal anti-inflammatory drugs and risk of first hospital admission for heart failure in the general population.** *Heart* 2006, **92:**1610–1615.
18. Wolfe MM, Lichtenstein DR, Singh G: **Gastrointestinal toxicity of non-steroidal anti-inflammatory drugs.** *N Engl J Med* 1999, **340:**1888–1899.
19. Singh G, Ramey DR, Morfeld D, et al.: **Gastrointestinal tract complications of non-steroidal anti-inflammatory drug treatment in rheumatoid arthritis: a prospective observational cohort study.** *Arch Intern Med* 1996, **156:**1530–1536.
20. Singh G, Triadafilopoulus G: **Epidemiology of NSAID-induced GI complications.** *Rheumatology* 1999, **26(Suppl l):**18–24.
21. Lichtenstein DR, Syngal S, Wolfe MM: **Non-steroidal anti-inflammatory drugs and the gastrointestinal tract: the double-edged sword.** *Arthritis Rheum* 1995, **38:**5–18.
22. Hernandez-Diaz S, Rodriguez LAG: **Association between non-steroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s.** *Arch Intern Med* 2000, **160:**2093–2099.
23. Lanas A, Garcia-Rodriguez LA, Arroyo MT, et al.: **Risk of upper gastrointestinal ulcer bleeding associated with cyclo-oxygenase 2 inhibitors, traditional non-steroidal anti-inflammatory drugs, aspirin and combinations.** *Gut* 2006, **55:**1731–1738.

24. Singh G, Wang H, Mithal A, et al.: **Comparing apples with oranges: choice of comparator non-selective NSAIDs alters the gastrointestinal safety advantages of COX2 inhibitors in clinical trials of arthritis patients [abstract SAT0264]. Presented at the Annual European Congress of Rheumatology, Barcelona 2007.** *Ann Rheum Dis* 2007, **66(Suppl II):**510.
25. Singh G, Triadafilopoulos G: **Appropriate choice of proton pump inhibitor therapy in the prevention and management of NSAID-related gastrointestinal damage.** *Int J Clin Pract* 2005, **59:**1210–1217.
26. Ibanez I, Vendrell L, Moretti U, et al.: **Upper gastrointestinal bleeding associated with anti-platelet drugs.** *Aliment Pharmacol Ther* 2006, **23:**235–242.
27. Rostom A, Dube C, Wells G, et al.: **Prevention of NSAID-induced gastroduodenal ulcers.** *Cochrane Database Syst Rev* 2002, **4:**CD002296.
28. Chan FK, Chung SC, Suen BY, et al.: **Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low dose aspirin or naproxen.** *N Engl J Med* 2001, **344:**967–973.
29. Hinz B, Brune K: **Cyclooxygenase2--10 years later.** *J Pharmacol Exp Ther* 2002, **300:**367–375.
30. Fitzgerald GA: **Coxibs and cardiovascular disease.** *N Engl J Med* 2004, **351:**1709–1711.
31. Bombardier C, Laine L, Reicin A, et al.: **Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis.** *N Engl J Med* 2000, **343:**1520–1528.
32. Bresalier RS, Sandler RS, Quan H, et al.: **Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial.** *N Engl J Med* 2005, **352:**1081–1091.
33. Solomon SD, McMurray JJ, Pfeffer MA, et al.: **Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention.** *N Engl J Med* 2005, **352:**1071–1090.
34. **FDA statement on stopping Celebrex trial. December 17, 2004.** Available at http://www.fda.gov.bbs/topics/news/2004/NEW01144.html. Accessed July 2007.
35. **EMEA press release on non-selective NSAIDs. August 2, 2005.** Available at http://www.emea.eu.int/pdfs/human/press/pr/24732305en.pdf. Accessed July 2007.
36. **MHRA release: cardiovascular safety of NSAIDS--review of the evidence.** Available at http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dID=1428&noSaveAs=0&Rendition=WEB. Accessed July 2007.
37. Andersohn F, Suissa S, Garbe E: **Use of first- and second-generation cyclo-oxygenase-2-selective non-steroidal anti-inflammatory drugs and risk of acute myocardial infarction.** *Circulation* 2006, **113:**1950–1957.
38. Andersohn F, Schade R, Suissa S, Garbe E: **Cyclo-oygenase-2 selective non-steroidal anti-inflammatory drugs and the risk of ischaemic stroke.** *Stroke* 2006, **37:**1725–1730.
39. Singh G, Mannalithara A, Wang H, et al.: **When COX2 selectivity does not matter: risk of stroke with NSAIDs in patients with arthritis [abstract SAT0264]. Presented at the Annual European Congress of Rheumatology, Barcelona 2007.** *Ann Rheum Dis* 2007, **66(Suppl II):**510.
40. Siverstien FE, Faich G, Goldstein JL, et al.: **Gastrointestinal toxicity with celecoxib vs. non-steroidal anti-inflammatory drugs for osteoarthritis: the CLASS study: a randomised controlled trial.** *JAMA* 2000, **284:**1247–1255.
41. Singh G, Fort JG, Goldstein JL, et al.: **Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I study.** *Am J Med* 2006, **119:**255–266.
42. Laine L, Curtis SP, Cryer B, et al.: **Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison.** *Lancet* 2007, **369:**465–473.
43. Bertagnolli MM, Eagle CJ, Zauber AG, et al.: **Celecoxib for the prevention of sporadic colorectal adenomas.** *N Engl J Med* 2006, **355:**873–884.
44. Arber N, Eagle C, Spicak J, et al.: **Celecoxib for the prevention of colorectal adenomatous polyps.** *N Engl J Med* 2006, **355:**885–895.
45. Antman EA, Bennett JS, Daugherty A, et al.: **Use of non-steroidal anti-inflammatory drugs, an update for clinicians. A scientific statement from the American Heart Association.** *Circulation* 2007, **115:**1634–1642.

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Update on the use of analgesics versus nonsteroidal anti-inflammatory drugs in rheumatic disorders: risks and benefits

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Purpose of review

In the last 2 years, there have been numerous publications on the safety of nonsteroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors. An evaluation of the potential risks and benefits of other analgesics has also followed. In this time of greater analysis of analgesic use, this study seeks to present the most recent evidence.

Recent findings

Concerns of potential hepatotoxicity of therapeutic doses of paracetamol have been highlighted in the last 18 months. The ongoing efficacy and risks of long-term opioid use has also been reevaluated. The debate over nonsteroidal anti-inflammatory drug and cyclo-oxygenase-2 inhibitor safety continues.

Summary

Recent evidence has prompted a reassessment of the safety of paracetamol in certain groups of patients. Further clarification on the risks of nonsteroidal anti-inflammatory drug and cyclo-oxygenase-2 therapy for individuals is covered. Their use, increased cardiovascular risk and long-term implications need to be evaluated.

Keywords

arthritis, nonsteroidal anti-inflammatory drugs, opioids, pain, paracetamol

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Introduction

Systemic pain control in rheumatic diseases is achieved by combining the use of peripherally and centrally acting analgesics, along with nonsteroidal anti-inflammatory drugs (NSAIDs) and drugs that modify the underlying disease process. Recently, concerns over the safety and toxicity of analgesics and NSAIDs have been raised. We review studies that have highlighted these issues over the last 18 months.

Pain control in the rheumatic disorders

The impact of poorly controlled pain on our patients is far-reaching. Eighty-eight percent of female respondents in a rheumatoid arthritis (RA) study in Ireland reported that pain was their major health impairment [1]. Deterioration in health status as a result of pain was a common perception. The link between pain and psychological symptoms cannot be ignored: a cohort of 238 patients was reviewed from this perspective [2]. Thirty percent of the respondents had a visual analogue scale pain score of more than 40 mm. Five to thirteen percent had high depression scores but 20–30% had high anxiety scores. It is thus advised that pain-related outcomes should be studied in more detail by researchers.

Acetaminophen/paracetamol

Acetaminophen or paracetamol is the first-line analgesic recommended by the American College of Rheumatology for the treatment of osteoarthritis [3]. Although its exact mode of action remains unclear, it is thought to cause selective inhibition of prostaglandins within the central nervous system and cause peripheral analgesia. It has been shown to reduce the production of prostaglandin E2 [4•]. Interestingly, a recently published study shows that paracetamol inhibits cyclo-oxygenase-2 (COX2) to a degree comparable with NSAIDs and COX2 inhibitors. COX1 blockade of more than 95%, important for a cardioprotective effect by platelet suppression, was not achieved [5].

The onset of action of paracetamol is approximately 30 min with a short terminal elimination phase half-life (approximately 2 h after therapeutic doses). It therefore requires to be taken frequently, with a maximum of 1 g four times daily. Longer acting preparations, such as 650 or 1300 mg extended release three times daily, have been evaluated. One such study [6•] confirmed that a total of 3900 mg extended release reduced Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain and physical function scores compared with placebo in patients with

osteoarthritis pain of hip or knee. There was no comparison with multiple dosing of standard tablets.

Paracetamol and hepatic abnormalities

Paracetamol first prepared commercially in 1950 in the United States. It was not until 1966 that concerns were raised that overdose, with its narrow therapeutic window, could cause hepatotoxicity and nephrotoxicity. Unintentional overdose of paracetamol has become one of the most important causes of acute liver failure; subsequently, a limit has been imposed on the amount of paracetamol that can be purchased over the counter in the United Kingdom.

Recently, concerns have been published on the potential of liver injury with therapeutic paracetamol doses. It has been demonstrated that patients with viral hepatitis who were given standard doses of paracetamol had an additional increase in transaminases and prothrombin time [7]. The hepatotoxic potential of paracetamol is thought to be influenced by a number of factors including microsome-inducing drugs, underlying disease, malnutrition, acute or chronic alcohol use, ethnicity and age.

Watkins *et al.* [8] have looked into the effects of therapeutic paracetamol doses on transaminases either alone or in combination with opioids. They designed a randomized single-blinded placebo controlled trial in which 145 healthy adult volunteers were randomized to five parallel treatment groups: placebo, paracetamol, paracetamol and morphine, paracetamol and hydromorphone, and paracetamol and oxycodone. All received standardized, catered meals; none had access to alcohol for the 14-day study duration. Of the 39 patients in the placebo group, only one had an elevation of serum alanine aminotransferase (ALT) greater than five times the baseline value. Over 19% of the 105 participants in the active groups, however, had an ALT greater than five times the baseline value. This was in the absence of a plasma paracetamol level that would be considered hepatotoxic. In all cases, ALT decreased to normal on completion of the study.

Further work is required on the potential hepatotoxicity of therapeutic doses of paracetamol. This has particular implications on patients who misuse alcohol, are malnourished and are on therapies that may induce liver enzymes [9].

Paracetamol and renal function

The Nurses Health study [10] examined the association of 'lifetime intake of paracetamol' and change in estimated glomerular filtration rate (eGFR) over an 11-year period. Those who took at least 3000 g of paracetamol had a multivariate adjusted odds ratio of 2.19 ($P < 0.001$) for reduction of 30 l/min or more of eGFR compared with those who took less than 100 g over the period (odds ratio 1.00, referent). Patients with established renal impairment were not specifically studied and this warrants further assessment in future studies.

Paracetamol and gastrointestinal side effects

Little has been recently published on this controversial subject. A nested case–control study [11] used information from the UK General Practice Research Database in the1990s. Paracetamol exposure was ascertained for those patients who had suffered upper gastrointestinal complications. Analysis of 1494 cases and 9532 controls was performed. Paracetamol use was associated with small elevated risk of upper gastrointestinal complications: relative risk (RR) 1.3 (95% CI: 1.1–1.5). RR increased to 3.6 if more than 2 g paracetamol was consumed per day. Patients who took both NSAIDs and paracetamol at doses higher than 2 g per day had a RR of 13.2 (95% CI: 9.2–18.9) compared with those who did not use either of these drugs. Paracetamol, however, could have been given preferentially to patients with a history of dyspepsia or peptic ulcer disease.

Paracetamol and hypertension

Analysis of the Nurses Health Study II [12] demonstrated that more than 500 mg per day of paracetamol was associated with a higher risk of incident hypertension (multivariate RR 1.99, $P < 0.001$). The Health Professionals Follow-Up study [13••] looked at associations between frequency of paracetamol, NSAID and aspirin use and the risk of hypertension during a 4-year period. Frequency of analgesic use at baseline and at 2 years was recorded for sixteen thousand and thirty-one male health professionals who did not have a history of hypertension at baseline. One thousand nine hundred and sixty-eight cases of incident hypertension during 4 years of follow-up were identified. Men who used paracetamol six or seven times per week had a multivariable adjusted RR of hypertension of 1.34 (95% CI: 1.00–1.79) compared with nonusers ($P = 0.01$ for trend). The association between paracetamol and risk of hypertension was greater in men with a body mass index of less than 25; the mechanisms for this are unclear. One would anticipate that given that all participants were health professionals, the self-reported 'hypertension' label would be fairly reliable. The fact that patients took regular doses of analgesics may be an additional confounding factor in this analysis.

Nonsteroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors

When rofecoxib was withdrawn in 2004, much was published in medical and lay press on the potential risks of anti-inflammatory therapies. Since then, the number of publications on this subject has continued to increase.

Cardiovascular risk

Several meta-analyses [14–16] of observational studies have concluded that the risk of myocardial infarction (MI) differs between individual NSAIDs and COX2s. McGettigan and Henry [17] confirmed that diclofenac had a relative risk of 1.4 (95% confidence interval = 1.16–1.7), which is higher than that for other traditional NSAIDs.

Hepatic risk

Back in the 1980s, a number of NSAIDs were withdrawn because of cases of fatal hepatotoxicity. A recent review [18] of adverse drug reactions in France confirmed that 14% of all NSAID reports were for abnormal liver function. Two lumiracoxib-related studies published in *Lancet* in 2004 [19,20] reported a reduction in gastrointestinal ulcer complications and no apparent evidence of increased risk of MI. In November 2007, however, the Medicines and Healthcare products Regulatory Authority in the UK withdrew this drug because of 159 episodes recorded worldwide of adverse liver reactions attributed to this drug, two of which were fatal [21]. These publications emphasize the importance of prompt review of patients on NSAID or COX2 who develop abnormal liver function and consideration given to immediate withdrawal of therapy.

Upper gastrointestinal risk

Serious gastrointestinal complications of NSAID use are well documented in the medical literature. There is now considerable evidence to suggest that the gastrointestinal toxicity profiles of NSAIDs differ. Lanas *et al.* [22] found that naproxen was associated with the highest risk of gastrointestinal bleeding (RR = 7.3, 95% CI: 4.7–11.4). The combination of NSAID and low-dose aspirin increased the risk even further (RR = 12.7, 95% CI: 7–23). Diclofenac and ibuprofen were observed to have the lowest risk of gastrointestinal bleeding. A recently published study [23••] evaluated the combination of COX2 and proton pump inhibitor (PPI) in patients with upper gastrointestinal bleeding secondary to NSAID-induced ulceration. Two hundred and seventy-three patients were randomized to celecoxib and esomperazole combination or placebo. None of the patients who received COX2 and PPI combination had further upper gastrointestinal bleeding, whereas 12 of the patients who received celecoxib alone had bleeding ($P = 0.0004$). This study suggests a review of the guidelines of PPI prescription in those requiring a COX2 who are at high risk of further gastrointestinal bleeding. A limitation of this study is the lack of nonselective NSAID comparator. Details of the coprescription of aspirin in the context of cardiovascular risk were also missing from data analysis.

An algorithm incorporating NSAIDs and COX2s to aid decision making in pain management has been proposed in an excellent study [24••]. The authors propose choosing a therapy that provides good pain relief, minimizes cardiovascular risk as much as possible and preserves the gastrointestinal mucosa; no mean task. If acetaminophen is insufficient and NSAIDs are felt to be unsuitable for the patient, alternative analgesics should be used. If NSAIDs are appropriate, those with a low risk of gastrointestinal bleeding should have ibuprofen prescribed and then naproxen in case of inadequate benefit. Paracetamol and/or opioid can be used in a stepwise progression. They suggest that those at risk of gastrointestinal bleeding should have NSAID prescribed with PPI cover.

Nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors and aspirin coprescription

The use of aspirin in primary and secondary cardioprotection is well established. Aspirin irreversibly inhibits COX1-mediated production of thromboxane A2 (TXA2); 95% inhibition of TXA2 completely inhibits platelet aggregation. NSAIDs reversibly inhibit COX1 in platelets and so the subsequent effects on platelet aggregation depends on the half-life of the individual anti-inflammatory. It has been demonstrated that ibuprofen given before aspirin inhibited the beneficial effects of irreversible platelet inhibition [25]. On the basis of this and other studies, the US Food and Drug Agency (FDA) issued a warning in September 2006 regarding the coadministration of aspirin and ibuprofen [26]. They recommend that aspirin should be taken before any NSAID or that the doses should be given separately. Earlier study [27] has shown aspirin and COX2 prescribed concomitantly can reduce the incidence of MI. There were concerns of the gastrointestinal effects of COX2 and aspirin versus NSAID and gastroprotection in those who were coprescribed aspirin. Endoscopic studies [28••] have shown that the incidence of gastrointestinal ulcers did not differ between patients on celecoxib and aspirin combination compared with those on NSAID, aspirin and PPI. It has therefore been suggested that the use of low-dose aspirin with COX2s is preferable to nonselective NSAIDs [29••], given similar anti-inflammatory properties, superior gastrointestinal tolerability and absence of interaction with aspirin.

Opioids

Opioids are considered essential for the control of severe pain. They can be classified as weak (codeine, dextropropoxyphene and tramadol) or strong (morphine and oxycodone). A meta-analysis [30] evaluating the analgesic effect of opioids in chronic noncancer pain demonstrated that all subgroups were better than placebo. One third of patients, however, abandoned the therapy because of side effects such as nausea (14%), constipation (9%) and drowsiness (6%). Solomon *et al.* [31] reviewed opiate use from a database of Medicare beneficiaries in Pennsylvania. Four percent of the patients with RA used opioids regularly during one calendar year (2001); up

to 24% used opioids at some point in the 6-year period of review. The most commonly prescribed preparations were tramadol, dextropropoxyphene, codeine and hydrocodone. An association between chronic opioid use and psychiatric medication coprescription was observed.

Tramadol

Tramadol is a weak opioid with serotonin-releasing and noradrenaline reuptake inhibitory properties. It is used to treat moderate to severe pain and has an advantage over codeine in that it has less effects on the gastrointestinal tract. Tramadol has no effect on the renal system but can lower seizure threshold. In clinical practice, tramadol is often prescribed for patients with rheumatic conditions in whom a combination analgesic such as paracetamol and low-dose codeine combination is ineffective. The *Oxford League Table* for the efficacy of oral analgesics in acute pain was created from information gathered from systematic reviews of randomized, double-blind, single-dose studies [32]. This table gives tramadol 50 mg a low ranking in efficacy; number needed to treat of approximately 8. This value is comparable with the value of number needed to treat in the range of 1.6–3.0 for a number of NSAIDs. The drawbacks of such an analysis of analgesic efficacy include the large variation in study size for each individual preparation. A Cochrane review analysed 11 randomized controlled trials of tramadol use in osteoarthritis [33]. One thousand and nineteen participants received tramadol and/or paracetamol, whereas 920 received placebo or active control. Patients randomized to tramadol had a 12% relative decrease in pain intensity from baseline. Side effects were reported relatively commonly; the most common were nausea, vomiting, dizziness, constipation, tiredness and headache. The number needed to harm for major adverse events was eight.

The efficacy and tolerability of tramadol and paracetamol combination tablets in patients with RA with pain inadequately controlled by NSAIDs and disease-modifying antirheumatic drugs (DMARDs) alone has been studied [34]. Mean daily pain relief scores by the end of week 1 were greater in the tramadol group compared with the placebo group ($P = 0.037$). There was a 19% discontinuation rate with tramadol: nausea and dizziness were the most commonly reported adverse events. Incremental dose titration of tramadol may be useful and may reduce discontinuation rates and side effects over a short introductory period, as shown in a 2-week intervention period by Choi *et al.* [35•]. It appears that tramadol, if tolerated, provides a helpful increment in the analgesic ladder for patients with rheumatic conditions.

Fentanyl patch

Fentanyl is usually given by the transdermal route as its intravenous form has a very short duration of action. Transdermal fentanyl patches provide continuous drug delivery (over a 3-day period) in a convenient manner that may aid patient compliance when compared with intermittent dosing with oral opioids.

Two recent studies examined the potential benefit of fentanyl in the rheumatic diseases. Langford *et al.* [36], in the first placebo-controlled trial of fentanyl in chronic nonmalignant pain, randomized patients fulfilling the American College of Rheumatology criteria of osteoarthritis of hip or knee who were awaiting joint replacement to either transdermal fentanyl ($n = 202$) or placebo ($n = 197$). Previously prescribed NSAIDs and paracetamol could continue. Fentanyl therapy was associated with significantly improved pain scores. Seventy-eight percent of those randomized to fentanyl reported at least one adverse event ($P < 0.001$ versus placebo), with nausea, vomiting and somnolence as most commonly reported. Fifty-five patients (26%) discontinued fentanyl secondary to side effects.

A second, prospective open-labelled study [37•] reviewed 226 patients with RA with 'severe pain'. Transdermal fentanyl patch was added to their ongoing RA therapy for 30 days and pain evaluated on an 11-point numerical scale. Fentanyl significantly reduced pain scores from 8.0 (7.82–8.18) to 4.0 (3.75–4.25). Mean functional impairment because of pain also decreased significantly from 'severe' to 'mild to moderate'. Seventeen percent of the study participants reported at least one adverse event, nausea and vomiting being the most frequent. In this study, 23 patients (10%) discontinued tramadol because of side effects. These studies have shown the potential benefit of fentanyl in controlling pain but have highlighted the frequency of discontinuation secondary to adverse effects.

Opioids for low back pain

A systematic study [38••] published the previous year reviewed the prevalence and effectiveness of opioid therapy in chronic back pain. The occurrence of substance misuse was also analysed. Eleven studies described the prevalence of opioid treatment for chronic back pain. Prescribing practice varied widely, ranging from 3 to 66%, with higher percentages seen in specialist treatment centres and lower prescription in primary care centres. Fifteen studies reviewed the efficacy of opioid treatment. The average opioid dose used (in morphine units) was 73 mg per day. Only four studies compared the efficacy of opioids with a nonopioid control or placebo. No significant reduction in pain with opioids was seen ($P = 0.136$). Lifetime substance misuse disorders ranged from 36 to 56%. An important fact highlighted by this systematic review is that no study evaluated the benefit of opioid prescription beyond 16 weeks; therefore, long-term efficacy is not known. A Cochrane review of opioids in chronic low back pain [39••] concludes that there are

few high-quality trials assessing their efficacy. The authors voice the same concerns as those expressed in the above studies in calling for high-quality studies of longer duration in this area.

A review [40••] of the evidence for medications in chronic low back pain by the American Pain Society and American College of Physicians clarified further the evidence for use of opioid in this condition. Both tramadol and

Table 1 Treatment options for pain related to the rheumatic disorders

Simple analgesia	Anti-inflammatories	Opioids	Other strategies
	No gastrointestinal or cardiovascular risk	First line: oral, weak opioids	Nonpharmacological
Paracetamol	Ibuprofen	Codeine	Lifestyle advice
1 g p.o. q.i.d.	400–600 mg p.o. t.i.d.	30–60 mg p.o. q.i.d.	Weight loss if appropriate
Anchor analgesic	Can be used in combination with paracetamol/cocodamol	Can be used with paracetamol	Footwear
Minimal gastrointestinal symptoms	Avoid concomitant administration with aspirin [25,26]	Commonly reported side effects include constipation and nausea	Walking aids
Risk of abnormal liver function tests at therapeutic doses [8,9]		Cocodamol (8/500 or 30/500)	Education
		Two tablets p.o. q.i.d.	Employment
		Step-up from paracetamol alone	Self-management schemes
		Commonly reported side effects include constipation and nausea	Exercise
		Tramadol	Physiotherapy
		50–100 mg p.o. q.i.d.	Acupuncture
		Commonly reported side effects include constipation and nausea [33,34,35•]	
	Gastrointestinal risk, no cardiovascular risk	Second line: stronger opioids	Local treatment
	Celecoxib	Transdermal fentanyl	Intra-articular steroid injection(s)
	200–400 mg p.o.	12–100 μg/h	Contra-indicated in sepsis
	Shown to have better gastroprotection than traditional NSAIDs	Change patch every 72 h	Topical NSAIDs or capsaicin
	Consider adding proton pump inhibitor if high risk gastrointestinal bleeding [23••].	Can be used with paracetamol	TENS machine
	Ibuprofen + PPI	Start at lowest dose and up-titrate if necessary	Surgical intervention for diseased joint
	For example, ibuprofen 400–600 mg p.o. t.i.d. and omeprazole 20 mg p.o. o.d.	Side effects of nausea and somnolence reported [36,37•]	If appropriate, for example, total knee replacement
		Oral morphine	
		For example, morphine sulfate tablets 20 mg p.o. b.i.d. + sevredol 5 mg p.o. p.r.n. for breakthrough pain	
	Cardiovascular and gastrointestinal risk		Management of underlying condition
	Each patient requires to be reviewed on an individual basis		Maximize DMARD therapy in rheumatoid arthritis: alone or in combination
	Avoid anti-inflammatories if possible or use lowest possible dose for shortest period of time		Guided as per symptoms, disease activity, blood monitoring and side-effects [41•,42]
	If patient on aspirin either naproxen or a COX2 selective agent would be preferable given similar anti-inflammatory properties, superior gastrointestinal tolerability and absence of interaction with aspirin [28••,29••]		Biologic therapy (anti-tumour necrosis factor)
			If patient meets guidelines for use in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis. Can reduce pain scores by reducing disease activity [43–46,47•]
			Amitriptyline 10–100 mg p.o. at night. Good for neuropathic pain or persisting pain that disturbs sleep

COX2, cyclo-oxygenase-2; DMARDs, disease-modifying antirheumatic drugs; NSAIDs, nonsteroidal anti-inflammatory drugs; p.r.n., according to circumstances; PIP, proton pump inhibitor; TENS, transcutaneous electrical nerve stimulator.

stronger opioids showed moderate net benefit, although only two of the 11 studies reviewed compared either drug with placebo. Their overall recommendations are that paracetamol should be tried first for mild to moderate back pain. For more severe pain, the benefits of improved analgesia from NSAIDs need to be balanced with the documented gastrointestinal and cardiovascular risks of such therapy. A trial of opioids is recommended for severe, disabling pain in properly selected patients. The authors conclude that treatment choices for low back pain should be made after considering the potential risk and benefit of such therapies for the individual patient.

Disease-modifying antirheumatic drugs and biologic therapies' effect on pain control

DMARDs and biologic therapies not only reduce synovitis but also slow disease progression, with concomitant reduction in pain. This, in turn, reduces the need for analgesics. The MASCOT study [41•] showed a reduction in pain score by a median of eight points when sulfasalazine and methotrexate combination was used. This was statistically significant when compared with patients on sulfasalazine alone ($P = 0.071$). The CAMERA study [42] reviewed the impact of intensive methotrexate treatment as guided by a strict protocol and computer program ($n = 92$) versus conventional methotrexate treatment ($n = 113$). There was a significant difference in pain score between the two groups by 3 months: intensive arm = 12 (interquartile range 5–24.3), conventional arm = 19 (9.5–34.1), $P = 0.001$.

Studies with adalimumab [43], etanercept [44], infliximab [45] and abatacept [46] in RA have all demonstrated improved pain control with a reduction in patient's assessment of pain on a visual analogue scale. A study [47•] specifically assessing patient's health status improvements with commencement of tumour necrosis factor-blocking agents has provided helpful confirmatory information in real-life prescribing. Arthritis Impact Measurement Scales 2 (AIMS2) arthritis pain scores at 3 and 6 months of anti-tumour necrosis factor therapy were significantly lower than the baseline values ($P < 0.05$). At baseline, 88% of patients listed pain as a priority for improvement; this decreased to 71% by 12 months. This study confirms that pain relief can be achieved with anti-tumour necrosis factor therapy and pain control remains the most important priority for patients with RA even after 12 months of treatment.

Conclusion

In the complex setting of choosing an analgesic for patients with rheumatic disorders, physicians need to take into account a number of issues including the patient's personal cardiovascular and gastrointestinal risks, the potential benefit of treatment and ultimately the cost-effectiveness of the chosen therapy. We hope to have illustrated the options for analgesia in this group of patients in a succinct tabular form (see Table 1). Further research is required into the long-term risks of hepatotoxicity and hypertension observed with long-term paracetamol use; especially, as this is the therapy most often used when the risk of anti-inflammatory drugs is deemed unacceptable.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1 Minnock P, FitzGerald O, Bresnihan B. Women with established rheumatoid arthritis perceive pain as the predominant impairment of health status. Rheumatology 2003; 42:995–1000.

2 Ødegård S, Finset A, Mowinckel P, *et al.* Pain and psychological health status over a 10-year period in patients with recent onset rheumatoid arthritis. Ann Rheum Dis 2007; 66:1195–1201.

3 American College of Rheumatology Subcommittee on osteoarthritis guidelines. Recommendations for medical management of hip and knee osteoarthritis: 2000 update. Arthritis Rheum 2000; 43:1905–1915.

4 • Lee Y-S, Hyungsuk K, Brahim JS, *et al.* Acetaminophen selectively suppresses peripheral prostaglandin E2 release and increases COX-2 gene expression in a clinical model of acute inflammation. Pain 2007; 129:279–286.

Although the results of this study come from an oral surgery background (extraction of impacted third molars), we can still extrapolate helpful information from their scientific work when paracetamol was compared with rofecoxib and ketorolac in terms of thromboxane2 and prostaglandin E2 release.

5 Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooygenase-2 inhibitor in man. FASEB J; doi: 10.1096/fj.07-8506com. Accessed 31 December 2007.

6 • Altman RD, Zinsenheim JR, Temple AR, Schweine JE. Three-month efficacy and safety of acetaminophen extended-release for osteoarthritis pain of the hip or knee: a randomised, double-blind, placebo-controlled study. Osteoarthritis Cartilage 2007; 15:454–461.

A study showing the potential benefit of extended release paracetamol preparation in patients with osteoarthritis over a 12 week period.

7 Yaghi C, Honein K, Boujaoude J, *et al.* Influence of acetaminophen at therapeutic doses on surrogate markers of severity of acute viral hepatitis. Gastroenterol Clin Biol 2006; 30:763–768.

8 Watkins PB, Kaplowitz N, Slattery JT, *et al.* Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily. JAMA 2006; 296:87–93.

9 Jalan R, Williams R, Bernuau J. Paracetamol: are therapeutic doses entirely safe? [comment]. Lancet 2006; 368:2195–2196.

10 Curhan GC, Knight EL, Rosner B, *et al.* Lifetime nonnarcotic analgesic use and decline in renal function in women. Arch Intern Med 2004; 164:1519–1524.

11 González-Pérez A, García Rodríguez LA. Upper gastrointestinal complications among users of paracetamol. Basic Clin Pharmacol Toxicol 2006; 98:297–303.

12 Forman JP, Stampfer MJ, Curhan GC. Nonnarcotic analgesic use and risk of incident hypertension in US women. Hypertension 2005; 46:500–507.

13 Forman JP, Rimm EB, Curhan GC. Frequency of analgesic use and risk of •• hypertension among men. Arch Intern Med 2007; 167:394–399.
Further detailed work from the team who have previously analysed the Nurses Health Study from a similar perspective. This study reports that frequent non-narcotic analgesic use is independently associated with a modest increase in risk of incident hypertension.

14 Singh G, Wu O, Langhorne P, Madhok R. Risk of acute myocardial infarction with nonselective nonsteroidal anti-inflammatory drugs: a meta-analysis. Arthritis Res Ther 2006; 8:R153.

15 Hernandez-Diaz S, Varas-Lorenzo C, García Rodríguez LA, *et al.* Nonsteroidal anti-inflammatory drugs and the risk of acute myocardial infarction. Basic Clin Pharmacol Toxicol 2006; 98:266–274.

16 Kearney PM, Baigent C, Godwin J, *et al.* Do selective cyclo-oxygenase-2-inhibitors and traditional nonsteroidal anti-inflammatory drugs increase the risk of atherothrombosis? BMJ 2006; 332:1302–1308.

17 McGettigan P, Henry D. Cardiovascular risk of inhibition of cyclo-oxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclo-oxygenase-2. JAMA 2006; 296:1633–1644.

18 Lapeyre-Mestre M, Rueda de Castro AM, Bareille M-P, *et al.* Nonsteroidal anti-inflammatory drug-related hepatic damage in France and Spain: analysis from national spontaneous reporting systems. Fundam Clin Pharmacol 2006; 20:391–395.

19 Schnitzer TJ, Burmester GR, Mysler E, *et al.* Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. Lancet 2004; 364:665–674.

20 Farkouh ME, Kirschner H, Harrington RA, *et al.* Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. Lancet 2004; 364:675–684.

21 Medicines and Healthcare products Regulatory Authority. Lumiracoxib (Prexige): suspension of marketing authorisation; 2007. www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2033073&ssTargetNodeId=221. Accessed 25 January 2008.

22 Lanas A, García Rodríguez LA, Arroyo MT, *et al.* Risk of upper gastrointestinal ulcer bleeding associated with selective COX-2 inhibitors, traditional non-aspirin NSAIDs, aspirin and combinations. Gut 2006; 55:1731–1738.

23 Chan FKL, Wong VWS, Suen BY, *et al.* Combination of a cyclo-oxygenase-2 •• inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. Lancet 2007; 369:1621–1626.
Further detailed analysis from a world-renowned unit on the subject of COX2s combined with proton pump inhibitor. Despite a lack on nonselective NSAID comparator, this study does add helpful information on the potential benefits of their co-prescription.

24 Ong CKS, Lirk P, Tan CH, Seymour RA. An evidence based update on •• nonsteroidal anti-inflammatory drugs. Clin Med Res 2007; 5:19–34.
A comprehensive review of NSAID efficacy and their adverse effects. The paper concludes with a helpful algorithm to aid decision-making in the use of analgesics in different clinical contexts.

25 Catella-Lawson F, Reilly M, Kapoor SC. Cylcooxygenase inhibitors and the antiplatelet effects of aspirin. N Eng J Med 2001; 345:1809–1817.

26 United States Food and Drug Agency. Information for healthcare professionals: concomitant use of ibuprofen and aspirin. Issued September 2006. http://www.fda.gov/cder/drug/InfoSheets/HCP/ibuprofen_aspirinHCP.htm. Accessed 31 December 2007.

27 Singh G, Graham D, Wang H, *et al.* Concomitant aspirin use reduces the risk of acute myocardial infarction in users of cyclo-oxygenase-2-selective and some nonselective nonsteroidal anti-inflammatory drugs. Ann Rheum Dis 2006; 65:S61.

28 Goldstein JL, Cryer B, Amer F, Hunt B. Celecoxib plus aspirin versus naproxen •• and lansoprazole plus aspirin: a randomized, double-blind, endoscopic trial. Clin Gastroenterol Hepatol 2007; 5:1167–1174.
A large endoscopic trial of 1045 patients with osteoarthritis. This showed that irrespective of prescribed aspirin dose. No difference in the occurrence of gastroduodenal ulcers was seen between NSAID and COX2 groups.

29 Strand V. Are COX-2 inhibitors preferable to nonselective nonsteroidal anti-•• inflammatory drugs in patients with risk of cardiovascular events taking low-dose aspirin? Lancet 2007; 370:2138–2151.
This is an in-depth and detailed review of the latest evidence and controversies surrounding COX2 and NSAID prescription, with regards to cardiovascular and gastrointestinal risks. An area of recent debate has been around the co-administration of aspirin and antiinflammatories and this is covered in detail with prescribing recommendations given.

30 Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ 2006; 174:1589–1594.

31 Solomon DG, Avorn J, Wang PS, *et al.* Prescription opioid use among older adults with arthritis or low back pain. Arthritis Rheum 2006; 55:35–41.

32 Oxford League Table of Analgesics in Acute Pain. Bandolier website http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/Leagtab.html. Accessed 31 December 2007.

33 Capeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. Cochrane Database of Systematic Reviews 2006; 3. Article No. CD005522. doi: 10.1002/14651858.CD005522.pub2.

34 Lee EY, Lee EB, Park BJ, *et al.* Tramadol 37.5 mg/acetaminophen 325 mg combination tablets added to regular therapy for rheumatoid arthritis pain: a 1 week randomised, double-blind, placebo-controlled trial. Clin Ther 2006; 28:2052–2060.

35 Choi C-B, Song JS, Kang YM, *et al.* A 2-week, multicenter, randomised, • double-blind, double-dummy, add-on study of the effects of titration on tolerability of tramadol/acetaminophen combination in Korean adults with knee osteoarthritis pain. Clin Ther 2007; 29:1381–1389.
In this, albeit short, study, up-titration of combination paracetamol/tramadol tablets was associated with lower side effects and subsequent lower discontinuation rates.

36 Langford R, McKenna F, Ratcliffe S, *et al.* Transdermal fentanyl for improvement of pain and functioning in osteoarthritis. A randomized, placebo-controlled trial. Arthritis Rheum 2006; 54:1829–1837.

37 Berliner MN, Giesecke T, Bornhölvd KD. Impact of transdermal fentanyl on • quality of life in rheumatoid arthritis. Clin J Pain 2007; 23:530–534.
One of the few recent studies evaluating the use of tramadol specifically in patients rheumatoid arthritis.

38 Martell BA, O'Connor PG, Kerns RD, *et al.* Systematic review: opioid treat-•• ment for chronic back pain: prevalence, efficacy and association with addiction. Ann Intern Med 2007; 146:116–127.
This is an extremely thorough study detailing the use of opioids in the treatment of low back pain. The links with dependence are discussed.

39 Deshpande A, Furlan A, Mallis-Gagnon A, *et al.* Opioids for chronic low-back •• pain. Cochrane Database of Systematic Reviews 2007; 3. Article No. CD004959. doi: 10.1002/14651858.CD004959.pub3.
A detailed analysis of the current evidence surrounding the use of opioids in chronic low-back pain. The authors conclude that further detailed studies are required to specifically evaluate the risks and benefits of such therapies in clinical practice.

40 Chou R, Huffman LH. Medications for acute and chronic low back pain: a •• review of the evidence for an American Pain society/American College of Physicians Clinical Practice Guideline. Ann Intern Med 2007; 147:505–514.
A detailed study analysing the evidence for different therapies in the treatment of both acute and chronic back pain, with information taken from systematic reviews and randomized trials. The authors conclude that one medication alone cannot be recommended because of the individualized nature of risk versus benefit in each patient.

41 Capell HA, Madhok R, Porter DR, *et al.* Combination therapy with sulfasalzine • and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalzine: results from the double-blind placebo-controlled MASCOT study. Ann Rheum Dis 2007; 66:235–241.
A useful study demonstrating the benefits of combination DMARD therapy with regards to hard-outcomes, such as disease activity and radiological changes, as well as patient reported symptoms of pain.

42 Verstappen SMM, Jacobs JWG, van der Veen MJ, *et al.* Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 2007; 66:1443–1449.

43 Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. Cochrane Database Syst Rev 2005; CD005113.

44 Genovese MC, Bathon JM, Fleischmann RM, *et al.* Longterm safety, efficacy and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. Rheumatology 2005; 32:1232–1242.

45 Lipsky PE, van der Heijde DMFM, St. Clair W, *et al.* Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000; 343:1594–1602.

46 Wienblatt M, Combe B, Covucci A, *et al.* Safety of the selective co-stimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs. A one-year randomized, placebo-controlled study. Arthritis Rheum 2006; 54:2807–2816.

47 Ten Klooster PM, Veehof M, Taal E, *et al.* Changes in priorities for improve-• ment in patients with rheumatoid arthritis during 1 year of antitumour necrosis factor treatment. Ann Rheum Dis 2007; 66:1485–1490.
This is a practical analysis of the impact of anti-tumour necrosis factor therapy on patient's pain control in RA. Importantly, it highlights that although pain may be better controlled with biologic therapy, it remains a very important concern for patients.

Therapeutics and Clinical Risk Management

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REVIEW

Celecoxib in arthritis: relative risk management profile and implications for patients

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Abstract: Celecoxib is a selective cyclo-oxygenase 2 inhibitor licensed for use in musculoskeletal symptoms as well as in primary dysmenorrhea and acute pain. One advantage celecoxib has over traditional nonsteroidal anti-inflammatory drugs is that of significantly fewer gastrointestinal side-effects associated with its use. Much has been published on the potential cardiovascular and cerebrovascular complications of its administration. This review details the available evidence to allow prescribers to make informed decisions in the light of potentially conflicting evidence. The overall cardiovascular risk is increased with higher doses of celecoxib but is comparable with nonselective nonsteroidal anti-inflammatory use. As with all of these drugs, the potential cardiovascular and gastrointestinal risks of prescription need to be weighed up against possible benefits for each individual patient and discussed with the patients themselves.

Keywords: arthritis, cardiovascular, celecoxib, gastrointestinal, nonsteroidal anti-inflammatory drugs, safety

Introduction

Celecoxib (Celebrex®; Pfizer Inc.) was the first selective cyclo-oxygenase (COX) 2 inhibitor to be used in everyday clinical practice. It is approved for use for musculoskeletal symptoms in osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis, as well as in the management of primary dysmenorrhea and acute pain. The advantages for selective COX2 inhibitor use has been well-documented in the literature; similar efficacy to nonsteroidal anti-inflammatory drugs (NSAIDs) but with less gastrointestinal (GI) side-effects. Celecoxib was the first of many selective COX2 inhibitors most of which have now been withdrawn from clinical use (lumiracoxib rofecoxib and valdecoxib) because of concerns of serious side-effects. This review will discuss the evidence for the potential benefits of celecoxib use as well as scrutinizing the studies which detail its possible deleterious effects.

Clinical effectiveness in treating arthritis

Multiple clinical trials have demonstrated that celecoxib has similar efficacy as nsNSAIDs in the management of pain and inflammation, both acute and chronic. Emery et al in 1999[1] studied the efficacy of celecoxib in patients with RA. Three hundred twenty-six patients received celecoxib 200 mg twice daily and 329 received diclofenac, a NSAID, 75 mg twice daily for 24 weeks. There was no documented difference between the 2 drugs for physician's assessment, patient assessment, number of swollen or tender joints, visual analogue scale (VAS) pain score, early morning stiffness, or C-reactive protein (CRP). The mean number of swollen and tender joints

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did however decrease over the course of the study. ACR-20 response at 24 weeks was scored as 25% in the celecoxib group and 22% in the diclofenac group. This paper was one of the initial studies to give credence to the use of celecoxib where traditional NSAIDs would have been used for the treatment of arthritis symptoms. In the same year a second group[2] undertook a randomized, placebo-controlled, double-blind trial with approximately 200 patients in each arm. Placebo was compared with naproxen 500 mg twice daily, celecoxib 100 mg twice daily, 200 mg twice daily, or 400 mg twice daily. Celecoxib produced a significant improvement in signs and symptoms of RA for all efficacy measures with maximal effects by 2 weeks and comparable with the benefits seen with naproxen. Withdrawals for treatment failure were lower for all active therapy groups than for placebo ($P < 0.001$).

A few years later, Deeks et al[3] performed a systematic review of the efficacy of celecoxib compared with another nonselective (ns) NSAID or placebo. Over 15,000 patients with either OA or RA who had received at least 12 weeks of therapy were identified. Efficacy was measured by the WOMAC score (Western Ontario and McMaster Osteoarthritis Index) and tolerability by rates of withdrawal for adverse events. Celecoxib and NSAIDs were equally effective for all efficacy outcomes. There were far fewer withdrawals in those taking celecoxib than other NSAIDs for GI side-effects.

A recently published review of celecoxib assessed the clinical and cost- effectiveness of selective COX2 inhibitors and NSAIDs for OA and RA treatment.[4] Forty randomized controlled trials involving celecoxib compared to placebo, other selective COX2 inhibitors, or nonselective (ns) NSAIDs were identified. Compared with nsNSAIDs, celecoxib was equally efficacious and of superior GI tolerability. The base-case incremental cost per quality adjusted life year (QALY) results for celecoxib versus diclofenac was £151,000.

Celecoxib and the upper gastrointestinal system

The GI toxicity of traditional NSAIDs is due to the nonselective inhibition of both COX1 and COX2 isoenzymes involved in prostaglandin synthesis.[5] Selective COX2 inhibitors were developed to suppress prostaglandin production by the COX2 enzyme selectively, consequently, giving anti-inflammatory and analgesic benefits while protecting the gastroprotective activity of COX1. The clinical adverse GI effects of NSAIDs are well known. Clinical symptoms are poor predictors of actual gastrointestinal injury. Anti-inflammatory drug-induced peptic ulcers are frequently asymptomatic. Patients taking traditional NSAIDs were previously said to be 5 to 7 times more likely to be hospitalized for a GI complication than nonusers.[6,7]

One of the first studies on the potential lesser upper GI effects of celecoxib was published in 1999.[2] Patients with RA were randomized to one of three differing doses of celecoxib (100 mg, 200 mg or 400 mg twice daily), naproxen or placebo. All doses of celecoxib were seen to have a reduced frequency of endoscopic ulcers than naproxen, the comparative NSAID in this study. Emery et al[1] demonstrated significantly reduced reporting of abdominal pain, gastric ulceration and duodenal ulceration when celecoxib was compared with diclofenac ($P < 0.05$, $P < 0.001$, and $P < 0.009$, respectively).

The celecoxib long-term arthritis safety study (CLASS) was a large double-blind randomized controlled trial. Patients with OA or RA were randomized to receive celecoxib 400 mg twice daily (n = 3987), ibuprofen 800 mg 3 times daily (n = 1985) or diclofenac 75 mg twice daily (n = 1996).[8] Initial data (at 6 months follow up) suggested that rates of symptomatic GI ulcers and ulcer complications were significantly lower with celecoxib compared with NSAIDs. However, full study results, when made available, showed that there was no difference at 1 year. The CLASS study had a high-dropout rate at 1 year which made the interpretation of these results somewhat difficult.

In 2002, Mamdani et al[9] performed a retrospective observational cohort study to compare rates of upper GI hemorrhage in elderly patients prescribed NSAIDs and selective COX2 inhibitors who were previously anti-inflammatory naïve. They found no increased short-term risk with celecoxib (adjusted rate ratio 1.0, 95% confidence interval [CI] 0.7 to 1.6), unlike NSAIDs and rofecoxib. The risk of upper GI hemorrhage with celecoxib was similar to that of controls not using NSAIDs. Singh et al[10] compared the GI side-effects of celecoxib with diclofenac and naproxen in a double-blinded, randomized clinical trial of over 13,000 patients (SUCCESS-I). Significantly more ulcer complications were seen in the NSAID than celecoxib group (0.8/1000-person years versus 0.1/1000-person years, odds ratio [OR] 7.02, $P = 0.008$).

van der Linden et al[11] performed a nested case-control study of a historical cohort of patients in The Netherlands to assess the incidence of first hospitalization for GI events in patient prescribed traditional NSAIDs and selective COX2 inhibitors (incorporating gastric and duodenal ulcers, ulceration of GI tract, gastritis, duodenitis, and GI hemorrhage). Adjusted OR for any GI with celecoxib therapy was 1.36 (95% CI 0.70 to 2.66). When compared with celecoxib, unsurprisingly, the risk was much higher with

the traditional NSAIDs, naproxen (OR 3.26, 95% CI 1.59 to 6.70) and diclofenac (OR 3.50, 95% 1.76 to 6.98).

Management difficulties can arise when patients are admitted with a GI bleed but require anti-inflammatory management for musculoskeletal symptoms. Chan et al published on recurrent ulcer bleeding rates in patients subsequently given celecoxib, who were initially admitted with upper GI bleeding while on a traditional NSAID for arthritis treatment.[12] Patients were either given celecoxib plus placebo or esomperazole, a proton-pump inhibitor (PPI). The combination group had a significantly reduced incidence of upper GI bleeding: 0 vs 12%, $P = 0.0004$, 95% CI 4.1 to 13.7.

Potential prevention of colorectal malignancies with celecoxib

The APC study investigators investigated the potential benefits of celecoxib on reducing colorectal adenomatous polyps and cancer.[13] This was on the basis that selective COX2 inhibitors had been shown to reduce the number of colorectal adenomas in animals, as well as that the over expression of COX2 had been associated with colorectal adenomatous polyps and cancer. Patients who had previously had adenomas removed were randomized to placebo, celecoxib 200 mg twice daily or 400 mg twice daily. The estimated cumulative incidence of detection of adenomas at year 3 was 43.2% in the 200 mg twice daily group (risk ratio [RR] 0.67, 95% CI 0.59 to 0.77, $P < 0.001$) and 37.5% in the 400 mg twice daily group (RR 0.55, 95% CI 0.48 to 0.64, $P < 0.001$) compared with placebo. For advanced adenomas in the two treatment groups the estimated cumulative incidence was 7.8% (RR 0.43, 95% CI 0.31 to 0.61, $P < 0.001$) and 6.3% (RR 0.34, 95% CI 0.24 to 0.50, $P < 0.001$) respectively.

In the same issue of the NEJM, the PreSAP trial investigators reported their randomized placebo controlled trial. They demonstrated that the use of 400 mg celecoxib once daily significantly reduced the occurrence of colorectal adenomas within the 3 years after a polypectomy (relative risk 0.64, 95% CI 0.56 to 0.75 $P < 0.001$).[14]

Potential hepatic side-effects

A number of individual case reports have been published detailing hepatoxicity secondary to celecoxib treatment.[15–17] More impressive however are the published data on larger-scale investigatory groups such as the CLASS study where nearly 4000 patients took celecoxib at 800 mg/day without any significant elevation in aminotransferases compared with traditional NSAID.[8] Importantly, the SUCCESS-1 study showed that the occurrence of transaminitis was much lower with celecoxib than with nsNSAIDs, 0.5% versus 1.3% ($P < 0.001$).[10] The FDA and WHO published a case/noncase analysis of spontaneous reports of hepatotoxicity of COX2s versus nsNSAIDs. The authors concluded that there was no increased safety concerns for celecoxib compared with NSAIDs, unlike diclofenac and nimesulide.[18] While we should be alert to the potential development of abnormal liver function while a patient is taking celecoxib, the major studies do not show any noteworthy trend.

Celecoxib and acute myocardial infarction

Concern was initially raised of the potential cardiovascular (CV) toxicity of selective COX2 inhibitors and NSAIDs was raised by the publication of data from the VIGOR trial by Bombardier et al[19] The CV risk of rofecoxib at that time was explained by being artefactual because of a presumed cardioprotective benefit of naproxen. Subsequent observational studies proved that this could not be true.[20] The first firm evidence demonstrating the increased risk of selective COX2 inhibitors compared with placebo was the APPROVe trial in 2004.[21] The results of this trial confirmed many previous observational studies on the CV risks of rofecoxib and lead to the withdrawal of the drug. Subsequently, the APC[13] and Pre-SAP[14] studies showed that at high doses, celecoxib can also increase the risk of CV complications when compared to placebo.

The risk of high doses of celecoxib was confirmed in a pooled analysis published by Solomon et al.[22] The data from 7950 patients enrolled in 6 placebo-controlled trials of celecoxib was analyzed. There was a clear increased risk of all CV events including acute myocardial infarction (AMI) with increasing doses of celecoxib ($P = 0.0005$). It should be noted that the patients in these studies had conditions other than arthritis. Many observational studies have shown that the increase in risk is not limited to celecoxib, but indeed is present with most nsNSAIDs[23] and that the risk with celecoxib may be of smaller magnitude than most other NSAIDs.[24] There are a large number of observational studies in publication in which these conclusions are also borne out.[4,11,25–30]

As mentioned previously, a large amount of data related to celecoxib and AMI is available from studies investigating the potential benefits in colorectal neoplasia prevention. The first data were published by Solomon et al in 2005.[31] Deaths from CV causes and nonfatal AMI numbered 27 in patients exposed to celecoxib, calculated hazard ratio (HR)

3.4 (nonfatal AMI alone numbered 18). A further paper published by Bertagnolli et al[13] the following year analyzed CV "disorders", encompassing a variety of conditions including AMI, angina, cerebrovascular disease, and circulatory collapse. RR in the whole group for low-dose celecoxib was 1.5, compared with 1.8 in higher doses.

The much referenced systematic review and meta-analysis from McGettigan and Henry[24] analyzed the risk of serious CV events with selective COX2 inhibitor therapy. They found that celecoxib was not associated with an increased risk of vascular occlusion (summary RR 1.06, 95% CI 0.91 to 1.23). This compares with summary RR of 1.33 for low-dose rofecoxib (95% CI 1.00 to 1.79), 2.19 for high-dose rofecoxib (95% CI 1.64 to 2.91), 1.40 for diclofenac (95% CI 1.16 to 1.70), 1.07 for ibuprofen (95% CI 0.97 to 1.18), and 0.97 for naproxen (95% CI 0.97 to 1.18).

As detailed from the many published works on this topic, the data on potential increased cardiovascular risk for patients taking celecoxib are inconsistent. It would seem clinically appropriate for the decision on prescription to be made on a patient by patient basis taking into account the individual's CV history and risk profile, and with regular reviews of the need for therapy. While inconsistent, the evidence most likely points to an increase in risk of AMI with celecoxib compared to placebo when doses of at least 400 mg are used. No clinical trials have been able to show an increased risk when 200 mg/day or less is used, although this does not rule out such an effect in susceptible patients. The increased risk does not seem to be out of proportion to the risk seen with nsNSAIDs.

Celecoxib and heart failure

Anti-inflammatory drugs can be associated with a degree of fluid retention through an increased cortical expression of COX2. Mamdani's population-based retrospective cohort study[32] assessed nearly 19000 NSAID-naïve patients who were commenced on celecoxib. Less than 1% developed congestive heart failure (CHF) within 6 months of commencement (identical to nonNSAID control group) and approximately 6% developed CHF over a 5-year period (not significant compared to the control group).

A population-based retrospective cohort study studied 2256 patients aged over 66 who were prescribed NSAID, rofecoxib or celecoxib after an index admission for CHF.[33] Crude event rates for recurrent CHF per 100 person-years were calculated and showed a difference between selective COX2 inhibitors (celecoxib 27.6, rofecoxib 32.4) and NSAIDs (24.4). Within the Colorectal Adenoma Prevention trial[31] the number of nonfatal heart failure events with the placebo group (n = 2, 0.3%) was comparable to the events in the celecoxib 200 mg bd group (n = 1, 0.1%). A case control study of patients admitted with congestive cardiac failure[34] identified 25 first admissions in patients prescribed celecoxib. Two of these patients had taken less than 600 mg celecoxib in the week prior to admission, 15 had taken between 601 and 1400 mg celecoxib, and 4 taken greater than 1400 mg. Multivariate analysis and comparison with controls showed a weak and statistically nonsignificant association between celecoxib use and hospitalization for CHF (OR 1.47, 95% CI 0.86 to 2.53, P = 0.160) – this was also seen for rofecoxib and other traditional NSAIDs.

Potential renal side-effects

The physiological interactions between COX2 and the renal system is complex. Increased cortical expression of COX2 is seen with sodium depletion, aortic coarctation, CHF, loop diuretic therapy and Bartter's syndrome amongst others. COX2 expression is specifically linked to the renin-angiotensin system (RAS) and causes activation of this pathway. Decreased RAS activity causes increased COX2 expression and vice versa. COX2 is known to have critical roles at the cortical thick ascending limb of the loop of Henle, macula densa and in the medullary interstitium.[35] There is case-report documentation of renal side-effects secondary to celecoxib use,[17] but much more robust data are available from a number of large-scale studies and reviews.

A randomized crossover trial of celecoxib with naproxen as the comparator looked specifically at renal function outcomes in an elderly population.[36] A comparable reduction in glomerular filtration rate was seen for both naproxen and celecoxib and therefore the selective COX2 inhibitor was not felt to be any more nephrotoxic. Similarly, the CLASS study did not show any significant elevation in serum creatinine in nearly 4000 celecoxib users when compared with NSAID users (ibuprofen or diclofenac).[8] Zhang et al published a large meta-analysis of 114 randomized, double-blind controlled trials of selective COX2 inhibitors, within which 37 celecoxib trial populations were identified.[37] The RR of developing renal dysfunction with celecoxib was 0.61 (95% CI 0.4 to 0.94) compared with controls. No between-treatment difference in creatinine clearance or serum electrolytes was seen in a double-blind, placebo-controlled study of 85 patients assigned to naproxen, etoricoxib, or celecoxib.[38]

As per prescribing guidelines, the use of celecoxib and NSAIDs is contra-indicated in patients with pre-existing renal impairment. The prescribing physician should remain alert to the development of abnormal renal function in a patient prescribed celecoxib, but its use is not associated with any increased nephrotoxicity compared with traditional NSAIDs.

Blood pressure effects of celecoxib

The effects of the addition of celecoxib on blood pressure (BP) control in patients on angiotension-converting enzyme inhibitors for hypertension has been studied via 24-hour ambulatory BP monitoring.[39] Doses of celecoxib 200 mg twice daily made no difference on the anti-hypertensive effect of lisinopril. Wolfe et al have published data on the association of NSAID use with hypertension.[40] In normotensive and hypertensive patients, there was no increased OR of higher documented BP with celecoxib. This was not the case for rofecoxib. Zhang's meta-analysis also failed to show any increased RR of hypertension with celecoxib therapy: 0.83.[37]

A number of meta-analyses have scrutinized the potential evidence connecting celecoxib with a rise in blood pressure. Aw et al published a meta-analysis in 2005 of 19 randomized control trials, which included 8 celecoxib trial populations.[41] Weighted mean differences (WMD) of systolic and diastolic BPs were calculated. Overall, a disproportionate increase in systolic rather than diastolic BP was seen with all nsNSAIDs. The overall RR of developing hypertension for celecoxib compared with placebo was not statistically significant (0.81, 95% CI 0.13 to 5.21). These data on hypertension compares well with the only other selective COX2 inhibitor still on the market, etoricoxib.

The CRESCENT investigators, lead by Sowers, did not show any difference with celecoxib on 24-hour ambulatory BP control in known hypertensives.[42] However, the proportion of patients with controlled blood pressure at baseline who developed worsening of BP by week 6 was documented as 16% in the celecoxib arm ($P = 0.05$), indicating that like all NSAIDs, BP monitoring is advised whenever treatment is initiated with celecoxib. Bertagnolli's work on the potential role in colorectal adenoma prevention of celecoxib documented some blood pressure data.[13] There was no significant increased RR of developing hypertension in the cohort and aspirin co-prescription made no difference. In contrast, Schwartz et al demonstrated a significant increase in ambulatory systolic BP with etoricoxib 90 mg once daily compared with celecoxib 200 mg twice daily and naproxen 500 mg twice daily ($P < 0.05$).[38] Additionally, recently published data from the MEDAL study documented an increase in systolic BP (average rise of 3.4 to 3.6 mmHg) with etoricoxib therapy.[43]

Celecoxib and stroke

Within the Colorectal Adenoma Prevention trial,[31] the number of nonfatal strokes with the placebo group was identical to the events in the celecoxib 200 mg twice daily group (n = 3, 0.4%), compared with 5 events (0.7%) in the celecoxib 400 mg twice daily group. Solomon et al's cohort study of over 26,000 celecoxib users in the Medicare program identified 988 strokes and an adjusted RR of 1.00 (95% CI 0.92 to 1.09).[29]

A landmark study from Andersohn and colleagues assessed nearly 500,000 patients on the UK GP research database between 2000 and 2004[44] to identify the risk of ischemic stroke with NSAID or selective COX2 inhibitor use. No increased risk was found with current celecoxib use (multivariate OR 1.07). An increased risk was seen with rofecoxib and etoricoxib (OR 1.71 and 2.38, respectively). As per the AMI data, a dose-dependent effect was seen. Celecoxib at ≤200 mg/day was associated with a multivariate OR 0.97 (95% CI 0.71 to 1.32) and >200 mg/day was associated with a multivariate OR 1.20 (95% CI 0.46 to 3.11). Etoricoxib at ≤60 mg/day was associated with a much higher multivariate OR 2.04 (95% CI 0.87 to 4.80) and >60 mg/day was associated with a multivariate OR 3.27 (95% CI 0.59 to 18.16). It is possible that these differences in stroke rates between celecoxib and etoricoxib reflect the differential effect on hypertension of these drugs.

Lee et al[45] reviewed the impact of celecoxib prescription on cerebrovascular disease incidence in patients with and without documented coronary artery disease (CAD). There was no increased risk of cerebrovascular event in the group without CAD prescribed celecoxib (OR 0.97, 95% CI 0.68 to 137). However, there was an increased risk of events in those with pre-existing CAD prescribed celecoxib (OR 1.40, 95% CI 0.96 to 2.03). A recently published study based on data from the population-based Rotterdam study[46] assessed HR for ischemic stroke with NSAID and selective COX2 inhibitor prescription. Only 1 event was documented in celecoxib users and therefore there was no significant outcome.

Nadareishvili et al[47] performed a nested case control analysis to determine the risk of stroke in patients with RA. Two hundred sixty-nine patients with first-ever stroke were identified, including 41 in patients with RA. The OR for

ischemic stroke in RA was 2.66 (95% CI 1.24 to 5.70, $P = 0.012$). Adjusted for cardiovascular, RA risk factors, and other co-variants, ischemic stroke was significantly associated with rofecoxib use (OR 3.66, $P = 0.27$), but not significantly with celecoxib (OR 2.65, $P = 0.051$). A recently published retrospective cohort study of over 300,000 Medicaid patients in Tennessee over a 5-year period[48] documented 4354 stroke admissions. Of these, 144 were patients who were prescribed celecoxib. Compared with nonusers of selective COX2 inhibitors or NSAIDs, the adjusted HR for stroke was only 1.04 (95% CI 0.87 to 1.23). A slightly higher HR of 1.12 (95% CI 0.83 to 1.52) in new users of celecoxib was documented.

Effects of co-prescription of celecoxib and aspirin

The benefit of aspirin in the primary and secondary prevention of CV events is well established. As the prescription rates for aspirin will continue to climb, the number of patients potentially prescribed this as well as an anti-inflammatory drug will too.

Wilner et al[49] published a double-blind, placebo-controlled trial of 16 healthy volunteers assigned to celecoxib 400 mg daily or placebo for 4 days. Aspirin 325 mg plus celecoxib 200 mg or placebo was prescribed on day 5. No significant difference in thromboxane inhibition between the 2 groups was noted. There was also no significant difference in the effect of aspirin on platelet aggregation due to ADP, collagen, or arachidonic acid between the groups. The groups summarized that celecoxib does not have an effect on the aspirin effects of platelet function. This is an important consideration in the selection of NSAIDs in patients on low-dose aspirin since, unlike celecoxib, several nsNSAIDs have been shown to cause pharmacodynamic interference with the anti-platelet effect of aspirin.

The population impact of any possible interaction is potentially large. In a sample of the general population prescribed selective COX2 inhibitors, analyzed by Cox et al[50] 48% were co-prescribed aspirin, 43% paracetamol, and, interestingly, 10% also were prescribed a nonselective NSAID. Unsurprisingly, the use of aspirin increased with increasing patient age.

Levesque[51] documented the RR of first AMI in a cohort of over 113,000 elderly patients. Patients prescribed celecoxib with or without aspirin were identified. There was no significant difference in adjusted RR of AMI in those who were or were not prescribed aspirin alongside celecoxib. This differs from the low-dose rofecoxib group who showed a significantly reduced risk of AMI if prescribed aspirin – the same was not true for patients on high-dose rofecoxib. It must be pointed out that the actual number of patients who had an AMI while on aspirin was small and conclusions drawn from this study should be guarded. Rahme et al found that the combination of celecoxib and aspirin was less likely to be associated with hospitalization for GI events than NSAIDs with aspirin (HR 0.62, 95% 0.48 to 0.80).[52,53] In fact, hospitalization rates for GI events were similar for celecoxib plus aspirin as NSAID without aspirin (HR 1.01, 95% CI 0.81 to 1.25). A limitation of the study was that over-the-counter data for aspirin were not available.

Conclusion

Celecoxib continues to be an effective and valuable alternative to traditional NSAIDs in the treatment of acute and chronic pain. The superior GI tolerability is well-documented and compelling. Data on potential increased CV risk for patients taking celecoxib are inconsistent, but do point to a small increase risk, especially when higher doses are prescribed. This risk is comparable with that of traditional nonselective NSAIDs.

As with all of these drugs, the potential CV and GI risks of prescription need to be weighed against possible benefits for each individual patient and discussed with the patient. If the CV risk increase with celecoxib is small and lower than that of most other NSAIDs, the concern would be of increasing the complications in a high CV risk patient if they were to be prescribed another NSAID. If such a high-risk patient must take aspirin, the argument for selective COX2 inhibitors is stronger as nsNSAIDs may block the effect of aspirin. Concomitant PPI use should be considered in these patients. As is the case with all anti-inflammatories, the prescription of celecoxib for an individual patient should be reviewed regularly and the lowest dose used for the shortest possible period of time.

Disclosures

The authors declare no conflicts of interest.

References

1. Emery P, Zeidler H, Kvien TK, Guslandi M, Naudin R, Stead H, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet*. 1999;354(9196):2106–2111.
2. Simon LS, Weaver AL, Graham DY, Kivitz AJ, Lipsky PE, Hubbard RC, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA*. 1999;282(20):1921–1928.
3. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: Systematic review of randomised controlled trials. *BMJ*. 2002;325(7365):619–623.

4. Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: A systematic review and economic evaluation. *Health Technol Assess (Rockv)*. 2008;12(11):iii–158.
5. Meade EA, Smith WL, DeWitt DL. Differential inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) isozymes by aspirin and other non-steroidal anti-inflammatory drugs. *J Biol Chem*. 1993;268(9):6610–6614.
6. Fries JF, Miller SR, Spitz PW, Williams CA, Hubert HB, Bloch DA. Toward an epidemiology of gastropathy associated with nonsteroidal antiinflammatory drug use. *Gastroenterology*. 1989;96(2 Pt 2 Suppl): 647–659.
7. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1999;340(24):1888–1899. [erratum in *N Engl J Med*. 1999;341(7):548].
8. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA*. 2000;284(10): 1247–1255.
9. Mamdani M, Rochon PA, Juurlink DN, Kopp A, Anderson GM, Naglie G, et al. Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs. *BMJ*. 2002;325(7365):624–627.
10. Singh G, Fort JG, Goldstein JL, Levy RA, Hanrahan PS, Bello AE, et al. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. *Am J Med*. 2006;119(3):255–266. [erratum in *Am J Med*. 2006;119(9):801].
11. van der Linden MW, van der Bij S, Welsing P, Kuipers EJ, Herings RMC. The balance between severe cardiovascular and gastrointestinal events among users of selective and non-selective non-steroidal anti-inflammatory drugs. *Ann Rheum Dis*. 2009;68:668–673.
12. Chan FK, Wong VW, Suen BY, Wu JC, Ching JY, Hung LC, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. *Lancet*. 2007;369(9573):1621–1626.
13. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, et al. Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med*. 2006;355(9):873–884.
14. Arber N, Eagle CJ, Spicak J, Racz I, Dite P, Hajer J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med*. 2006;355(9):885–895.
15. Galan MV, Gordon SC, Silverman AL. Celecoxib-induced cholestatic hepatitis. *Ann Intern Med*. 2001;134(3):254.
16. Grieco A, Miele L, Giorgi A, Civello IM, Gasbarrini G. Acute cholestatic hepatitis associated with celecoxib. *Ann Pharmacother*. 2002;36(12):1887–1889.
17. Tabibian JH, Tabibian N, Kaufman DM. Late-onset celecoxib-induced combined hepato-nephrotoxicity. *Br J Clin Pharmacol*. 2008;66(1):150–151.
18. Sanchez-Matienzo D, Arana A, Castellsague J, Perez-Gutthann S. Hepatic disorders in patients treated with COX-2 selective inhibitors or nonselective NSAIDs: A case/noncase analysis of spontaneous reports. *Clin Ther*. 2006;28(8):1123–1132.
19. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med*. 2000;343(21):1520–1528.
20. Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR. Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study. *Lancet*. 2002;359(9301): 118–123.
21. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med*. 2005;352(11): 1092–1102. [erratum in *N Engl J Med*. 2006;355(2):221].
22. Solomon SD, Wittes J, Finn PV, Fowler R, Viner J, Bertagnolli MM, et al. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: the cross trial safety analysis. *Circulation*. 2008;117(16): 2104–2113.
23. McKellar G, Madhok R, Singh G. The problem with NSAIDs: what data to believe? *Curr Pain Headache Rep*. 2007;11(6):423–427.
24. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA*. 2006;296(13):1633–1644.
25. Andersohn F, Suissa S, Garbe E. Use of first- and second-generation cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs and risk of acute myocardial infarction. *Circulation*. 2006;113(16):1950–1957.
26. Gislason GH, Jacobsen S, Rasmussen JN, Rasmussen S, Buch P, Friberg J, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation*. 2006;113(25):2906–2913.
27. Graham DJ, Campen D, Hui R, Spence M, Cheetham C, Levy G, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet*. 2005;365(9458):475–481.
28. Helin-Salmivaara A, Virtanen A, Vesalainen R, Gronroos JM, Klaukka T, Idanpaan-Heikkila JE, et al. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. *Eur Heart J*. 27(14):1657–1663.
29. Solomon DH, Avorn J, Sturmer T, Glynn RJ, Mogun H, Schneeweiss S. Cardiovascular outcomes in new users of coxibs and nonsteroidal antiinflammatory drugs: high-risk subgroups and time course of risk. *Arthritis Rheum*. 2006;54(5):1378–1389.
30. Hernandez-Diaz S, Varas-Lorenzo C, Garcia Rodriguez LA. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Basic Clin Pharmacol Toxicol*. 2006;98(3):266–274.
31. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med*. 2005;352(11):1071–1080.
32. Mamdani M, Juurlink DN, Lee DS, Rochon PA, Kopp A, Naglie G, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet*. 2004;363(9423): 1751–1756.
33. Hudson M, Richard H, Pilote L. Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study. *BMJ*. 2005;330(7504):1370.
34. McGettigan P, Han P, Jones L, Whitaker D, Henry D. Selective COX-2 inhibitors, NSAIDs and congestive heart failure: differences between new and recurrent cases. *Br J Clin Pharmacol*. 2008;65(6):927–934.
35. Harris CJ, Brater DC. Renal effects of cyclooxygenase-2 selective inhibitors. *Curr Opin Nephrol Hypertens*. 2001;10(5):603–610.
36. Whelton A, Schulman G, Wallemark C, Drower EJ, Isakson PC, Verburg KM, et al. Effects of celecoxib and naproxen on renal function in the elderly. *Arch Intern Med*. 2000;160(10):1465–1470.
37. Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. *JAMA*. 2006;296(13):1619–1632.
38. Schwartz JI, Thach C, Lasseter KC, Miller J, Hreniuk D, Hilliard DA, et al. Effects of etoricoxib and comparator nonsteroidal anti-inflammatory drugs on urinary sodium excretion, blood pressure, and other renal function indicators in elderly subjects consuming a controlled sodium diet. *J Clin Pharmacol*. 2007;47(12):1521–1531.

39. White WB, Kent J, Taylor A, Verburg KM, Lefkowith JB, Whelton A. Effects of celecoxib on ambulatory blood pressure in hypertensive patients on ACE inhibitors. *Hypertension*. 2002;39(4):929–934.
40. Wolfe F, Zhao S, Pettitt D. Blood pressure destabilization and edema among 8538 users of celecoxib, rofecoxib, and nonselective nonsteroidal antiinflammatory drugs (NSAID) and nonusers of NSAID receiving ordinary clinical care. *J Rheumatol*. 2004;31(6):1143–1151.
41. Aw TJ, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Arch Intern Med*. 2005;165(5):490–496.
42. Sowers JR, White WB, Pitt B, Whelton A, Simon LS, Winer N, et al. The Effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. *Arch Intern Med*. 2005;165(2):161–168. [erratum in *Arch Intern Med*. 2005;165(5):551].
43. Krum H, Swergold G, Curtis SP, et al. Factors associated with blood pressure changes in patients receiving diclofenac or etoricoxib: results from the MEDAL study. *J Hypertens*. 2009;27(4):886–893.
44. Andersohn F, Schade R, Suissa S, Garbe E. Cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs and the risk of ischemic stroke: a nested case-control study. *Stroke*. 2006;37(7):1725–1730.
45. Lee TA, Bartle B, Weiss KB. Impact of NSAIDS on mortality and the effect of preexisting coronary artery disease in US veterans. *Am J Med*. 2007;120(1):98.e9–e16.
46. Haag MD, Bos MJ, Hofman A, Koudstaal PJ, Breteler MM, Stricker BH. Cyclooxygenase selectivity of nonsteroidal anti-inflammatory drugs and risk of stroke. *Arch Intern Med*. 2008;168(11):1219–1224.
47. Nadareishvili Z, Michaud K, Hallenbeck JM, Wolfe F. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case-control study. *Arthritis Rheum*. 2008;59(8):1090–1096.
48. Roumie CL, Mitchel EF Jr, Kaltenbach L, Arbogast PG, Gideon P, Griffin MR. Nonaspirin NSAIDs, cyclooxygenase 2 inhibitors, and the risk for stroke. *Stroke*. 2008;39(7):2037–2045.
49. Wilner KD, Rushing M, Walden C, Adler R, Eskra J, Noveck R, et al. Celecoxib does not affect the antiplatelet activity of aspirin in healthy volunteers. *J Clin Pharmacol*. 2002;42(9):1027–1030.
50. Cox ER, Frisse M, Behm A, Fairman KA. Over-the-counter pain reliever and aspirin use within a sample of long-term cyclooxygenase 2 users. *Arch Intern Med*. 2004;164(11):1243–1246.
51. Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults. *Ann Intern Med*. 2005;142(7):481–489.
52. Rahme E, Nedjar H. Risks and benefits of COX-2 inhibitors vs non-selective NSAIDs: does their cardiovascular risk exceed their gastrointestinal benefit? A retrospective cohort study. *Rheumatology*. 46(3):435–438.
53. Rahme E, Bardou M, Dasgupta K, Toubouti Y, Ghosn J, Barkun AN. Hospitalization for gastrointestinal bleeding associated with non-steroidal anti-inflammatory drugs among elderly patients using low-dose aspirin: a retrospective cohort study. *Rheumatology*. 2007;46(2):265–272.

Role for TNF in atherosclerosis? Lessons from autoimmune disease

Gayle E. McKellar, David W. McCarey, Naveed Sattar and Iain B. McInnes

Abstract | Inflammatory pathways have been implicated in the initiation and progression of cardiovascular diseases. Accelerated atherosclerosis has been described in patients with chronic inflammatory diseases, particularly rheumatoid arthritis, disproportionate to individuals' detectable traditional vascular risk factors. This finding suggests that other pathways associated with inflammation might account for increased vascular risk in such diseases. Highly specific biologic agents can precisely block the activity of cytokines generated during inflammatory cascades; the effects of these inflammatory moieties on vascular physiology and overall risk of cardiovascular events has been directly evaluated. This Review summarizes key epidemiologic, physiologic and model data, which together suggest that tumor necrosis factor, a pivotal cytokine in the inflammatory cascade, is directly involved in vascular pathophysiology and that its inhibition might confer an overall advantage to the recipient. Moreover, such data obtained in chronic inflammatory diseases likely have relevance to primary atherosclerosis.

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Introduction

Inflammatory pathways are considered of fundamental importance to atherogenesis initiation and propagation, and to the acute events that precede myocardial infarction and stroke. In parallel, it has been increasingly recognized that patients with chronic inflammatory disorders such as rheumatoid arthritis (RA) and psoriasis exhibit higher than expected rates of cardiovascular disease morbidity and mortality that, at least in the context of RA, cannot be explained by traditional risk factors alone. Thus, these diseases might offer a unique insight into the capacity of inflammatory pathways to directly influence vascular pathology. In particular, the revolution in the use of biologic agents to target inflammatory cytokines in a highly specific manner provides molecular scalpels with which to dissect the role of specific cytokines in vascular disease, at the levels of both the individual patient and the population. In this Review, we discuss the accelerated comorbidity of atherosclerosis associated with autoimmune diseases, using RA as an exemplar condition, as well as the immunobiology of tumor necrosis factor (TNF) in the context of atherogenesis. The evidence pertaining to vascular outcomes associated with TNF blockade, obtained primarily from small clinical trials that investigated changes in vascular pathology and physiology, as well as from observational studies, is discussed. Finally, we speculate on the implications of these studies and the broader effects of inflammation modifiers on vascular disease for the development of novel, inflammation-targeted therapeutics.

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Competing interests
G. E. McKellar declares associations with the following company: Abbott. D. W. McCarey declares associations with the following companies: Abbott and Wyeth. N. Sattar declares associations with the following companies: Abbott and Roche. I. B. McInnes declares associations with the following companies: Abbott, Schering and Wyeth. See the article online for full details of the relationships.

Cytokines in chronic inflammatory diseases

Cytokines are small glycoproteins that function primarily as messengers in the immune system via autocrine, paracrine or endocrine manners. Cytokines bind specific receptor complexes, which, in turn, signal via increasingly well-characterized signal transduction pathways to modulate gene expression within target cells. More than 100 cytokines within large, structurally related superfamilies have been described, and these mediate a large variety of regulatory and effector functions within the immune system and beyond. Cytokines tend to be regulated in a coordinated manner, facilitating their effector functions as an integrated cascade; however, some cytokines seem to occupy pivotal positions within this hierarchy, and hence offer important therapeutic opportunities.[1] TNF is a homotrimeric cytokine that binds to two receptors, TNFRI and TNFRII, and can thereby influence a variety of molecular and cellular events that contribute to several disease states.[2] After synthesis in the endoplasmic reticulum, TNF is trafficked to the cell membrane where it remains as a functional membrane protein, or is solubilized via the action of a membrane-bound cleaving enzyme, TNFα converting enzyme (TACE; Figure 1). TNF regulates leukocyte activation, maturation, cytokine and chemokine release, and production of reactive oxygen and nitrogen intermediates (Figure 2). As such, it is a central regulator of inflammatory cascades during both initiation and amplification of

inflammatory reactions. TNF activates endothelial cells to express adhesion molecules as well as proinflammatory cytokine and chemokine receptors, and promotes synthesis and release of a variety of inflammatory cytokines and chemokines to thereby support recruitment of activated leukocytes to an inflammatory lesion. TNF probably promotes the inflammatory cascade within the arterial wall during development of atherosclerosis, in part by promoting endothelial cell injury.[3] It might directly promote endothelial cell apoptosis and suppress the activities of endothelial cell progenitors that could sustain endothelial repair.[4] TNF has also been implicated in promoting endothelial injury through recruitment of immune cells, such as neutrophils, which can mediate tissue destruction.[5] In addition, TNF promotes oxidative stress, and can directly impair nitric oxide bioavailability with consequent promotion of endothelial dysfunction. TNF impairs hemostasis, for example, by promoting the expression of tissue factor. It is a critical regulator of the acute phase response, acting in part via induction of interleukin (IL)-6 release. TNF has been implicated in the functional modulation of a variety of other tissue-specific cell types, including chondrocytes, osteoclasts, hepatocytes, neurons and adipocytes. Through the latter cell type, TNF might contribute to regulation of lipid and glucose metabolism,[6,7] which has direct clinical implications in the acute setting, for necessary advantageous metabolic responses to injury or severe infection, and in the chronic setting, for increased vascular risk. As such, TNF is considered a pleiotropic inflammatory cytokine with a central role in many pathophysiologic states and in associated comorbidities that affect more than just the primary target tissue.

Key points

- A variety of chronic inflammatory disorders confer increased risk of cardiovascular disease and attendant early mortality
- Tumor necrosis factor (TNF) is a key cytokine that mediates effector pathways in both inflammatory disease target tissues and in atherosclerotic vessels
- Clinical TNF blockade for treating inflammatory arthritis modulates vascular risk factors, generally in a beneficial direction, but there is a need for further data
- Epidemiologic data suggest that TNF blockade, and inflammatory suppression in general, might have beneficial effects on vascular outcomes in patients with inflammatory arthritis; however, definitive data are lacking
- Current data do not support the use of TNF antagonists as the primary intervention for the treatment or prevention of cardiovascular disease

Inflammatory arthritis and vascular risk

RA is a common arthropathy associated with articular synovial and bone marrow inflammation, cartilage and bone destruction, and consequent functional and social decline. It has been known for some time that RA is associated with reduced life expectancy, which cannot be explained only by the presence of traditional vascular risk factors.[8] A study conducted in our own center described 50% mortality over a 20 year follow-up period in 123 patients with RA, primarily as a result of cardiovascular disease.[9] A pooled analysis of the major studies available on the mortality of individuals with RA yielded a standardized mortality ratio of 1.70, with cardiovascular causes found to predominate in all studies.[8] A Scandinavian study, which followed 606 patients for 15 years, derived a standardized mortality ratio specific to cardiovascular disease of 1.46,[10] while a North American study by del Rincón *et al.* noted an approximate four-fold increase in cardiovascular events relative to the general population in 236 patients with RA over a period of 8 years.[11] Critically, del Rincón's study showed that the increase in vascular risk could not be accounted for by traditional cardiovascular risk factors, such as diabetes mellitus, smoking status, and hypercholesterolemia. This lends credence to the notion that RA or, perhaps, a high-grade, systemic inflammatory state *per se,* potentially along with a specific genetic component,[12] confers predisposition to the pathogenesis of atherosclerotic disease, or at least accelerates the disease process in affected individuals, acting as an independent risk factor.[13] Perhaps the best evidence for increased vascular risk comes from a meta-analysis of observational studies, which suggests that individuals with RA have a 50% higher risk of mortality related to cardiovascular disease than the general population.[14] Evidence from ultrasonography studies of carotid intima–media thickness (cIMT) in patients with RA without clinical evidence of atherosclerotic disease supports this concept as well; extra-articular disease and C-reactive protein (CRP) levels near the time of RA onset were both correlated with greater cIMT.[15] It is likely that this inflammatory amplification of vascular risk is mediated both by direct and indirect effects. For example, high levels of systemic cytokines can contribute directly to endothelial dysfunction and a state of hypercoagulation,[13] but can also indirectly contribute to vascular disease by influencing the qualitative nature of lipid particles.[16]

Inflamed synovium and unstable atherosclerotic plaque are strikingly similar in a number of respects. In both diseased tissues, elevated levels of cytokines, such as TNF, IL-6, IL-12, IL-15 and IL-18, have been observed, reflecting local stimulation of macrophages by activated T cells. In addition, the T cells implicated in the pathogenesis of atherosclerosis are predominantly of T_H1 or T_H17 phenotypes, which mirrors the pattern observed in active RA.[17] Both lesions contain an exaggerated matrix response and involve local cellular components, including respectively, synovial fibroblasts, chondrocytes and osteoclasts, and vascular smooth muscle, fibroblast and endothelial cells.[18] High levels of matrix metalloproteinases are expressed in both lesions. These parallels suggest possible mechanisms whereby patients with RA develop an increased risk of atherosclerosis and early death. The increased background level of chronic inflammation might confer predisposition to cardiovascular disease and/or augment its pathogenesis and put an individual at greater risk of developing an acute coronary syndrome or suffering secondary complications thereafter.

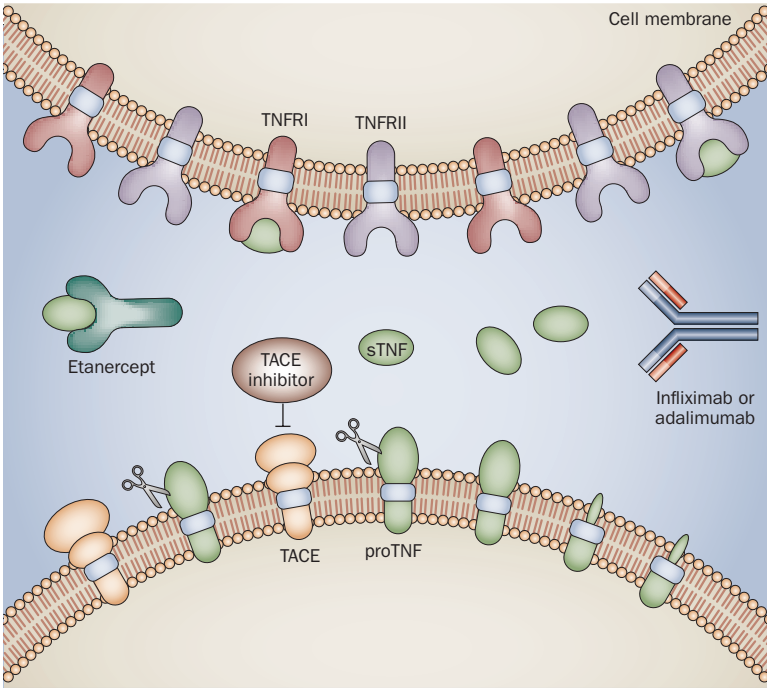

Figure 1 | TNF remains on the cell membrane as a functional membrane protein, or is solubilized via the action of a membrane-bound cleaving enzyme (TACE). It can thereby influence a variety of molecular and cellular events that contribute to several disease states. Anti-TNF therapies, such as etanercept, infliximab and adalimumab, bind to TNF and prevent the molecule from interacting with its two receptors, TNFRI and TNFRII, thus stopping signaling events. These large inhibitor molecules prevent binding of either sTNF or proTNF to their membrane receptor targets. Abbreviations: sTNF, soluble TNF; TACE, TNFα converting enzyme; TNF, tumor necrosis factor; TNFRI, TNF receptor I; TNFRII, TNF receptor II. Permission obtained from Nature Publishing Group © Moss, L. M., Sklair-Tavron, L. & Nudelman, R. *Nat. Clin. Pract. Rheum.* **4**, 300–309 (2008).

Much interest has focused on strategies to reduce vascular risk in RA. Most authorities now agree that such strategies must encompass aggressive modification of traditional vascular risk factors (at least as well as these same risk factors are managed in the general population) and optimal inflammatory disease control, aiming for clinical remission and normalization of inflammatory parameters. The introduction of biologic therapies, and specifically TNF antagonists, to the rheumatologist's therapeutic armamentarium has made the latter a realistic objective. Data suggest that targeting this key inflammatory cytokine, central to both disease processes, might also be effective in reducing vascular disease in patients with RA.

TNF in RA and atherosclerosis

Arguably the single greatest advance in the management of RA in recent times has been the identification of the key role of TNF in its pathogenesis. A multitude of proinflammatory and anti-inflammatory mediators has been characterized in the rheumatoid synovium but, among these, TNF, as identified in late 1982,[19] seems to be pivotal. TNF is localized in the lining layer and at the cartilage pannus junction. *In vitro* administration of neutralizing anti-TNF antibody to primary RA synovial cultures results in a marked reduction in local cytokine production.[20] Transgenic mice that express human TNF develop an inflammatory arthritis that is reminiscent of RA.[21] Furthermore, administration of anti-TNF antibody to DBA/1 mice with collagen-induced arthritis led to a substantial reduction in inflammation and damage.[22] This work led to the first human trials of infliximab, a chimeric monoclonal antibody that targets TNF, for treatment of RA—studies which demonstrated significant clinical benefit.[23]

Three TNF antagonists are currently licensed for the treatment of RA: infliximab, adalimumab (a fully humanized monoclonal antibody) and etanercept (a fusion protein of human soluble TNF receptor and the Fc component of human IgG1). All of these biologic agents have been shown to be effective in controlling disease activity, improving physical function and attenuating radiological progression in RA.[24–26] In addition, a number of studies have described the effects of these agents on vascular risk surrogates and rates of vascular disease.

Effects on endothelial dysfunction

Endothelial dysfunction has been touted as a possible early event in the evolution of atherogenesis, as well as a surrogate intermediate marker of risk of cardiovascular disease. A range of techniques aimed at estimating endothelial function have been employed, including plethysmography, ultrasonography-determined flow-mediated dilation (FMD), laser Doppler imaging with iontophoresis and more laterally, measures of pulse wave velocity (arterial stiffness) and pulse wave analyses. Reduced forearm blood flow has been demonstrated in studies where patients with either RA or systemic vasculitis who were taking standard RA therapy were compared with healthy controls.[27,28] In 2007, Gonzalez-Juanatey *et al.*[29] observed that flow mediated endothelium-dependent vasodilation was significantly impaired in individuals with psoriatic arthritis compared to controls ($P = 0.008$). This body of work has confirmed that patients with inflammatory rheumatic conditions have evidence of endothelial dysfunction.

Moreover, observational studies have demonstrated that TNF has an important role in endothelial dysfunction, and subsequent clinical trials have assessed the potential benefits of anti-TNF therapy for ameliorating this disease process. One of the first groups to investigate the effects of anti-TNF on endothelial function studied 11 patients with RA receiving infliximab.[30] A significantly increased FMD ($P = 0.018$), significant reductions in erythrocyte sedimentation rate ($P = 0.04$), CRP ($P = 0.08$) and disease activity score ($P = 0.002$), and no associated change in endothelium-independent vasodilation were demonstrated. Another study of infliximab for RA confirmed an increased FMD after first intravenous infusion (3.7 versus 17.5%, $P < 0.01$), with similar results following the second and third infusions.[31]

Effects on arterial stiffness

Arterial stiffness can be measured noninvasively. Pulse wave velocity (PWV) is a measure of the speed at which the arterial pressure wave travels. Higher values are associated with established cardiovascular risk factors and with cardiovascular mortality.[32] Augmentation index (AIx) is a quantitative index of systemic arterial compliance that refers to the difference between the first and second systolic peak of the central waveform, expressed as a percentage of the pulse pressure.[33] In a prospective study of 465 consecutive males undergoing coronary angiography, higher AIx was associated with an increased risk for coronary artery disease (multivariate analysis: odds ratio [OR] 6.91, P <0.05, 95% CI 1.41–33.70).[34]

Analysis of the association between RA and arterial stiffness has confirmed an increased aortic (carotid to femoral) PWV compared with controls (P = 0.005), and similar increased brachial (carotid to radial) PWV (P = 0.02), with no significant difference in augmentation index or augmentation pressure observed.[35] More recently, Avalos *et al.* observed that patients with a disease duration of greater than 10 years had a significantly higher AIx than patients with a disease duration of less than 5 years (P = 0.008) or controls (P <0.001)—an association that remained significant even after adjusting for cardiovascular risk factors (P = 0.02).[36]

Ongoing studies over the last 4 years have assessed the effect of anti-TNF therapy on arterial elasticity in RA. Van Doornum and her group did not detect a significant change in AIx in 14 anti-TNF-naive patients with RA who underwent 6 weeks of biologic therapy.[37] The same group had previously shown a significant reduction in AIx in a cohort of 29 patients with RA who received 20 mg atorvastatin daily for 12 weeks (P = 0.0002).[38] Further study in this area has produced corroborative results; commencement of etanercept in a group of 9 patients with RA lead to a reduction in disease activity score, CRP and erythrocyte sedimentation rate as well as aortic PWV (P = 0.0003) along with an increased FMD (P = 0.003), but no significant change in augmentation index.[35]

It seems that anti-TNF therapy might reduce PWV but have less, if any, affect on Alx; however, the current data are limited by the small cohorts studied.

Carotid intima–media thickness

Noninvasive B-mode ultrasonography of the carotid arterial system is now an FDA-approved surrogate marker of vascular disease for the purposes of clinical trials of therapies for coronary heart disease. cIMT is increased in patients with inflammatory conditions such as RA, psoriatic arthritis and systemic lupus erythematosus,[39,40] with cIMT severity associated with inflammatory burden and disease duration.[40] Studies are ongoing regarding the potential relationship between carotid plaque and these variables.

Gonzalez-Juanatey and colleagues failed to demonstrate a significant difference between the control group given standard therapy and a cohort of patients switched from standard RA treatment to infliximab; cIMT progression was not significantly different between the groups.[41] A more recent small study identified 30 patients with RA commencing anti-TNF (14 on infliximab, 16 on etanercept) and compared their disease progression and cIMTs over the course of a year's therapy with 10 controls. Anti-TNF therapy was associated with a significant and remarkable reduction in cIMT after one year of treatment (P <0.0001); a significant correlation between disease activity score in 44 joints and cIMT was also found (r = 0.435, P <0.05).[42] However, owing to the limitations of the currently available studies, larger, well-designed trials are needed to establish the true extent of benefit of anti-TNF therapies on cIMT.

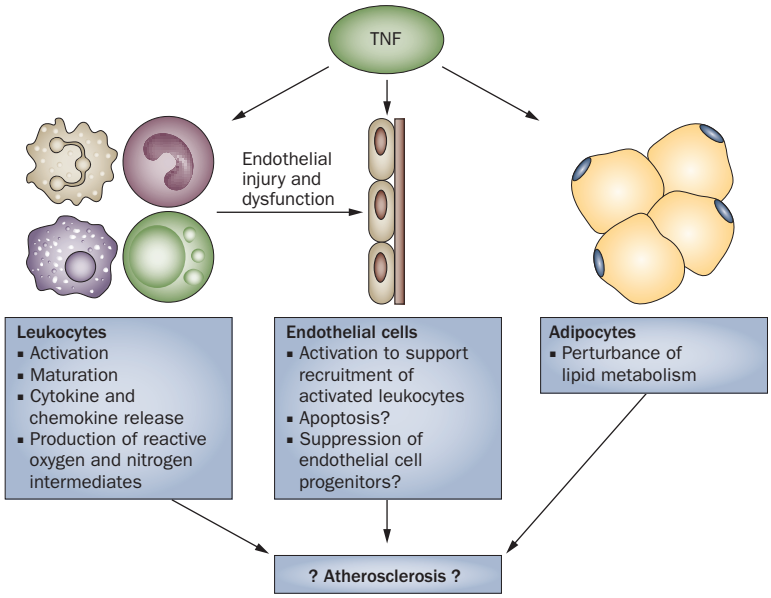

Figure 2 | TNF might cause atherosclerosis through actions on leukocytes, endothelial cells and adipocytes. Abbreviation: TNF, tumor necrosis factor.

Insulin sensitivity and obesity

A number of studies have confirmed an association between obesity, increased insulin sensitivity and elevated TNF levels.[43,44] Investigators have confirmed an improvement in insulin sensitivity with infliximab therapy in both patients with RA and those with ankylosing spondylitis.[45–47] Kiortis *et al.* demonstrated that those patients with the highest tertile of insulin resistance had the greatest reduction in HOMA (HOmeostasis Model Assessment, negatively correlated with insulin sensitivity; P <0.01) and the greatest increase in QUICKI (Quantitative Insulin Sensitivity Check Index; P <0.01).[47] Once again, however, such studies have been small and larger studies are required to improve the evidence base. Additionally, it should be noted that the wealth of prior studies suggest at best a modest association between insulin resistance (as measured by fasting insulin) and risk for vascular events.[48]

Table 1 | Lipid changes with anti-TNF treatments in autoimmune conditions

Study	Patients	Treatment and dosing	Changes in lipids
Allanore *et al.*[50]	Patients with RA[a] *n*=59	3 mg/kg infliximab Weeks 0, 2, 6, 14, 22, 30	↑ Total cholesterol ↑ HDL-C ↑ LDL-C ↔ Triglyceride ↔ Total cholesterol/HDL-C ↔ LDL/HDL-C
Vis *et al.*[51]	Patients with RA[b] *n*=69	3 mg/kg infliximab Weeks 0, 2, 6	↑ Total cholesterol ↑ HDL-C ↔ Total cholesterol/HDL-C
Popa *et al.*[52]	Patients with RA *n*=33	Adalimumab (dose not specified) Weeks 0, 2	↑ HDL-C ↔ LDL-C ↔ Triglyceride
Sattar *et al.*[53]	Patients with psoriatic arthritis *n*=126	100 mg onercept 3 times weekly for 12 weeks with placebo control	↔ Total cholesterol but ↑ apo B[c] ↔ HDL-C but ↑ apo A-I ↑ Triglyceride
Peters *et al.*[54]	Patients with RA *n*=80	3 mg/kg infliximab Weeks 0, 2, 6, and every 8 weeks thereafter	↑ Total cholesterol ↑ HDL-C ↑ Triglyceride ↓ Total cholesterol/HDL-C
Popa *et al.*[55]	Patients with RA *n*=67	3 mg/kg infliximab Weeks 0, 2, 6 and every 8 weeks thereafter	↑ Total cholesterol ↑ HDL-C ↑ LDL-C ↔ Triglyceride ↔ Total cholesterol/HDL-C ↔ LDL/HDL-C

[a]Exclusions: lipid lowering therapy, diabetes mellitus, hypothyroidism, alcoholism, chronic liver disease, Cushing syndrome. [b]Active RA, 32 patients on steroids at baseline. [c]Apo B and apo A-I are the main proteins in LDL-C and HDL-C particles, respectively. The apo B:apo A-I ratio is potentially more strongly linked to cardiovascular disease risk than the total cholesterol:HDL-C ratio. Abbreviations: Apo A-1, apolipoprotein A-1; apo B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

Biologic agents and lipid profiles

In the general population, it is well established that elevated cholesterol and low HDL-cholesterol levels are predictive of vascular event risk. The ratio of elevated total cholesterol to HDL cholesterol is thus reflective of lipid-associated vascular risk and is incorporated into many cardiovascular risk algorithms, for example the Joint British Societies' guidelines.[49]

Disease-modifying antirheumatic drug therapy has been associated with changes in lipid levels in multiple studies, as summarized in Table 1. Infliximab has been shown to significantly increase total cholesterol and HDL-cholesterol levels in patients with RA,[50,51] as has adalimumab.[52] A double-blinded, placebo-controlled trial of anti-TNF (onercept 50 mg or 100 mg) for treating psoriatic arthritis demonstrated significantly increased circulating levels of apolipoprotein A-I ($P = 0.002$), which is the main antiatherogenic protein in HDL particles. Significantly increased levels of triglycerides and apolipoprotein-B, the main protein in LDL particles, were also noted, which was an unexpected outcome and suggests that the biochemical lipid changes associated with anti-TNF therapies might be more complicated than originally thought.[53] Interestingly, significant reductions in homocysteine (–1.72 versus 0.34 mol/l with placebo) and lipoprotein(a) (–3.11 versus 1.52 mg/dl with placebo) were noted with TNF blockade. Further studies[54,55] suggest that treatment with anti-TNF leads to increases not only in HDL cholesterol, but also other lipid moieties, including total and LDL cholesterol, and perhaps triglycerides. Such changes in lipid levels might be the predictable response to attenuation of inflammation, because in untreated RA reductions in HDL cholesterol, LDL cholesterol and total cholesterol have been noted.[56] Moreover, these changes mirror lipid profile modifications associated with other pathologies/conditions that involve inflammation or infection, such as sepsis, cancer, trauma or post-operation.[57–59] Qualitative changes in lipid particles during inflammation complicate further interpretations, but it seems as if TNF blockade reverses many of the antiatherogenic effects of inflammation upon HDL particles.[16,60] Continued research on the nature and extent of lipids changes with biologics is needed.

In 2008, Jick *et al.* published a case–control study that evaluated whether statins were associated with a protective effect on the development of RA.[61] Patients with hyperlipidemia who were taking statins were less likely to develop RA than untreated patients (OR 0.59, 95% CI 0.37–0.96).

Biologic registry data

A number of large registries of patients with rheumatic conditions receiving biologic therapies have been established, with aims of producing long-term data on efficacy and toxicity. These registries include the South Swedish Arthritis Treatment Group (SSATG), the British Society for Rheumatology Biologics Register (BSRBR) and the German biologics register (RABBIT). Published data from the latter on the risk of heart failure with anti-TNF therapy has been discussed previously.[62]

In 2005, Jacobsson and colleagues from SSATG published the available data on the first incidence of cardiovascular events and deaths related to cardiovascular disease in patients included in their registry.[63] In the cohort of 531 patients exposed to anti-TNF, 13 such events, including 2 deaths, occurred. In parallel, 85 cardiovascular events, including 12 deaths, occurred among 543 control patients not exposed to anti-TNF therapy from a similar RA registry in Malmö, Sweden. The age–sex adjusted incidence rate of the first cardiovascular event among the anti-TNF-treated patients was 14 per 1,000 person-years (95% CI 5.7–22.4) compared with 35.4 per 1,000 person-years (95% CI 15.5–55.4) in the anti-TNF-naive group. However, the small sample size did not allow subgrouping for individual cardiovascular events, and data on lipid profiles, smoking status and blood pressure were lacking in this report.

The BSRBR conducted a UK-wide, prospective, observational study of patients commencing anti-TNF therapy, with a comparator group of biologic-drug-naive patients with active RA.[64] First-line analysis of the data confirmed a reduced rate of myocardial infarction in patients treated with anti-TNF (4.8 per 1,000 years)

compared with those individuals only treated with disease-modifying antirheumatic drugs (5.9 per 1,000 years). The BSRBR patients who had received anti-TNF were then assigned into 'responder' or 'non-responder' groups ($n = 5,877$ and $n = 1,638$, respectively). Further analysis after this categorization demonstrated a significantly lower incidence of myocardial infarction in the anti-TNF responders: 3.5 per 1,000 person-years versus 9.4 per 1,000 person-years (95% CI 2.5–4.9 and 5.5–15.0, respectively). Dixon *et al.* also reviewed the incidence of cerebrovascular accidents in patients from the same registry.[65] The crude incidence of cerebrovascular accidents was 3.9 per 1,000 years in the anti-TNF group (95% CI 2.9–5.3) and 9.9 per 1,000 years in the control (disease-modifying antirheumatic drugs) group (95% CI 5.3–16.9).

The information presented from registry databases has demonstrated results that broadly support the hypothesis that anti-TNF therapy might lessen cardiovascular risk, potentially through a reduction in inflammatory load.

Heart failure

TNF, along with other inflammatory molecules, is known to alter cardiac function through a number of mechanisms.[66] Levine and colleagues were one of the first groups to document the significantly elevated levels of TNF in a cohort of patients with chronic heart failure compared with controls.[67] Clinical trials to evaluate the efficacy of anti-TNF therapy in patients with NYHA class II or greater heart failure (including ATTACH, RECOVER and RENAISSANCE), were halted prematurely owing to the lack of clinical benefit and worsening of the patients' conditions.[68,69] An initial case series of 47 patients with new onset or exacerbated heart failure secondary to anti-TNF therapy prompted a review of prescribing protocols,[70] and guidelines incorporated heart failure as exclusion to therapy.

It has previously been shown that patients with RA are at twice the risk of congestive heart failure than individuals without the disease.[71] Investigators reviewing data from a German registry of anti-TNF therapy found a 2.2% 3 year incidence of heart failure in patients with pre-existing cardiovascular disease and a 0.4% 3-year incidence in those without.[62] After adjusting for traditional cardiovascular risk factors, a nonsignificant risk remained for development of heart failure (adjusted hazard ratio 1.66, 95% CI 0.67–4.1, $P = 0.28$). A number of confounders can be found in this analysis, such as a lack of a standardized definition for heart failure, a small number of actual events, and the exclusion of smoking as a risk factor owing to the lack of available data.

Prospects for the future

The foregoing evidence, as summarized in Figure 3, clearly implicates TNF in the accelerated atherogenesis and other cardiovascular events associated with RA. Many data indicate that heart disease has also been linked to other autoimmune disorders, including psoriasis. Yet, the corollary

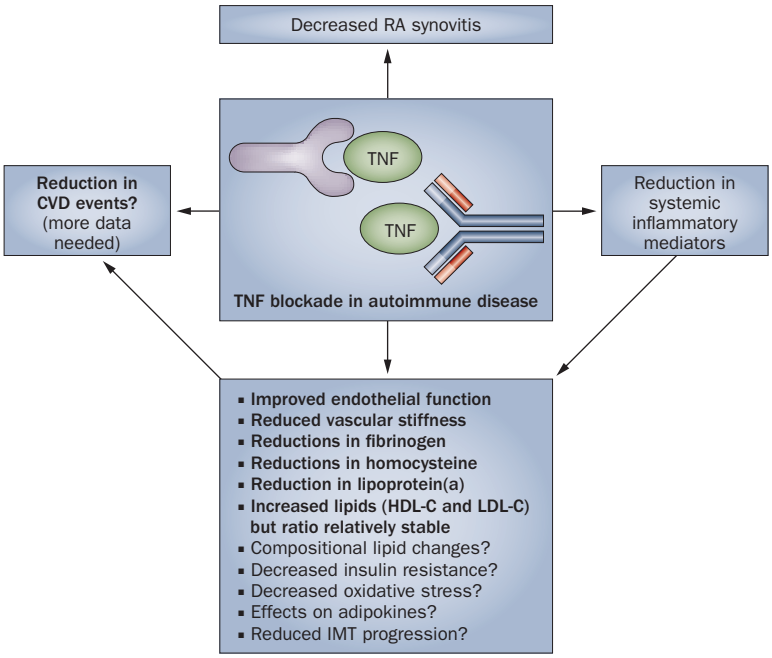

Figure 3 | Effects of TNF blockade on systemic inflammation, surrogate vascular and metabolic markers and CVD events. Abbreviations: CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; IMT, intima–media thickness; LDL-C, low-density lipoprotein cholesterol; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

to these associations might not be true, namely that TNF and related cytokines have a pivotal role in the pathogenesis of atherogenesis in nonautoimmune populations. Studies of commonly used therapeutics in the vascular therapeutic area suggest that inflammation modulation might be useful. Most evidence exists on the use of statins in primary and secondary preventative protocols, although most experts firmly believe that statin effects on outcomes (and possibly CRP) are mediated primarily via reduction in LDL cholesterol. Although large biologic therapeutics as currently investigated, or indeed envisaged, are unlikely to be appropriate for long-term vascular modification, they might be helpful in proof-of-concept studies. Moreover, small-molecule entities are being developed by many pharmaceutical companies, which should target cytokine effector pathways and thereby improve clinical outcomes. To this end, agents that target mitogen activated phosphokinases (for example, p38, JNK) or proximal signal transduction targets (for example, JAK1–3, syk kinase) are undergoing clinical development for treating a range of inflammatory disorders, particularly RA. If proven efficacious in inflammatory diseases *a priori*, such agents might provide an opportunity to formally test the potential of inflammation modulation in atherogenesis progression in the general population.

It will also be important to evaluate the effect of other novel biologic agents on vascular function, as well as their efficacy at treating autoimmune diseases. For example, intriguing phenomena are emerging with the advent of IL-6 blocking agents in RA that suppress disease activity

very effectively,[72] but that also lead to rapid and sustained, albeit modest in most cases, increases of cholesterol and triglyceride levels (as reviewed in 2009).[73] Whether such changes have any pathophysiologic significance is as yet unclear, although studies are underway to address these questions directly. The outcome of such studies should be informative not only to the relevant use of these agents in RA, but will also speak to the extensive vascular literature implicating IL-6 as a net proatherogenic factor. Indeed, other novel cytokines that might have a role, as implicated by vascular epidemiologic and pathophysiologic studies, could also be tested in the near future in this context—IL-17, IL-18, IL-12/IL-23 are all being investigated in clinical trials for managing RA and psoriasis, and vascular surrogates should be measured during their studies. Finally, the vascular effects of other types of RA treatments, such as cell targeting therapeutics, including abatacept (which modulates T cell costimulation via blockade of the CD28 and CD80/86 pathway), and rituximab (which selectively targets and depletes CD20-positive B cells),[74] will be submitted to detailed analysis.

In conclusion, considerable advances in understanding of the potential role of cytokines in atherogenesis have been made since the view of RA as an accelerated model of atherogenesis was proffered. Data from clinical TNF blockade have supported the principle that inflammation modulation can positively modulate vascular pathology. As the cytokine medicine field continues to broaden, attentive future analyses will demonstrate the general use of inflammation modulation in ameliorating primary vascular diseases.

Review criteria

We searched EMBASE, Medline and PubMed for articles published from 1980 to 2008, using the terms: "adalimumab", "anti-tumor necrosis factor", "arterial stiffness", "atherosclerosis", "cardiovascular disease", "carotid intima media thickness", "endothelial dysfunction", "etanercept", "heart failure", "inflammatory arthritis", "infliximab", "insulin sensitivity", "lipids", "psoriatic arthritis" and "rheumatoid arthritis". Full text articles, abstracts and meeting abstracts in the English language relating to human disease were selected for relevance. Reference lists were searched for further leads. References accessed from general reading (that is, not obtained through searches) were also included.

1. McInnes, I. B. & Schett, G. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat. Rev. Immunol.* **7**, 429–442 (2007).
2. Feldmann, M., Brennan, F. M. & Maini, R. N. Role of cytokines in rheumatoid arthritis. *Annu. Rev. Immunol.* **14**, 397–440 (1996).
3. Zhang, H. *et al.* Role of TNF-alpha in vascular dysfunction. *Clin. Sci. (Lond.).* **116**, 219–230 (2009).
4. Grisar, J. *et al.* Endothelial progenitor cells in active rheumatoid arthritis: effects of tumournecrosis factor and glucocorticoid therapy. *Ann. Rheum. Dis.* **66**, 1284–1288 (2007).
5. Quinn, K., Henriques, M., Parker, T., Slutsky, A. S. & Zhang, H. Human neutrophil peptides: a novel potential mediator of inflammatory cardiovascular diseases. *Am. J. Physiol. Heart Circ. Physiol.* **295**, H1817–H1824 (2008).
6. Zhao, S. P. & Dong, S. Z. Effect of tumor necrosis factor alpha on cholesterol efflux in adipocytes. *Clin. Chim. Acta* **389**, 67–71 (2008).
7. Nguyen, M. T. *et al.* JNK and tumor necrosis factor-alpha mediate free fatty acid-induced insulin resistance in 3T3-L1 adipocytes. *J. Biol. Chem.* **280**, 35361–35371 (2005).
8. Van Doornum, S., McColl, G. & Wicks, I. P. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? *Arthritis Rheum.* **46**, 862–873 (2002).
9. Capell, H., McCarey, D., Madhok, R. & Hampson, R. "5D" Outcome in 52 patients with rheumatoid arthritis surviving 20 years after initial disease modifying antirheumatic drug therapy. *J. Rheumatol.* **29**, 2099–2105 (2002).
10. Wallberg-Jonsson, S., Ohman, M. L. & Dahlqvist, S. R. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. *J. Rheumatol.* **24**, 445–451 (1997).
11. del Rincón, I. D., Williams, K., Stern, M. P., Freeman, G. L. & Escalante, A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum.* **44**, 2737–2745 (2001).
12. Gonzalez-Gay, M. A. *et al.* HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis Rheum.* **57**, 125–132 (2007).
13. Sattar, N., McCarey, D. W., Capell, H. & McInnes, I. B. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation* **108**, 2957–2963 (2003).
14. Aviña-Zubieta, J. A. *et al.* Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum.* **59**, 1690–1697 (2008).
15. Hannawi, S., Haluska, B., Marwick, T. H. & Thomas, R. Atherosclerotic disease is increased in recent-onset rheumatoid arthritis: a critical role for inflammation. *Arthritis Res. Ther.* **9**, R116 (2007).
16. Hahn, B. H., Grossman, J., Ansell, B. J., Skaggs, B. J. & McMahon, M. Altered lipoprotein metabolism in chronic inflammatory states: proinflammatory high-density lipoprotein and accelerated atherosclerosis in systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Res. Ther.* **10**, 213 (2008).
17. Cheng, X. *et al.* The Th17/Treg imbalance in patients with acute coronary syndrome. *Clin. Immunol.* **127**, 89–97 (2008).
18. Pasceri, V. & Yeh, E. T. A tale of two diseases: atherosclerosis and rheumatoid arthritis. *Circulation* **100**, 2124–2126 (1999).
19. Feldmann, M., Brennan, F. M. & Maini, R. N. Rheumatoid arthritis. *Cell* **85**, 307–310 (1996).
20. Brennan, F. M., Chantry, D., Jackson, A., Maini, R. & Feldmann, M. Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. *Lancet* **2**, 244–247 (1989).
21. Keffer, J. *et al.* Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis. *EMBO J.* **10**, 4025–4031 (1991).
22. Williams, R. O., Feldmann, M. & Maini, R. N. Anti-tumor necrosis factor ameliorates joint disease in murine collagen-induced arthritis. *Proc. Natl Acad. Sci. USA* **89**, 9784–9788 (1992).
23. Maini, R. *et al.* Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* **354**, 1932–1939 (1999).
24. Feldmann, M. & Maini, R. N. Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? *Annu. Rev. Immunol.* **19**, 163–196 (2001).
25. Bathon, J. M. *et al.* A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N. Engl. J. Med.* **343**, 1586–1593 (2000).
26. Weinblatt, M. E. *et al.* Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum.* **48**, 35–45 (2003).
27. Hänsel, S., Lässig, G., Pistrosch, F. & Passauer, J. Endothelial dysfunction in young patients with long-term rheumatoid arthritis and low disease activity. *Atherosclerosis* **170**, 177–180 (2003).
28. Booth, A. D. *et al.* Infliximab improves endothelial dysfunction in systemic vasculitis: a model of vascular inflammation. *Circulation* **109**, 1718–1723 (2004).
29. Gonzalez-Juanatey, C. *et al.* Endothelial dysfunction in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. *Arthritis Rheum.* **57**, 287–293 (2007).
30. Hürlimann, D. *et al.* Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. *Circulation* **106**, 2184–2187 (2002).

31. Irace, C. *et al.* Effect of anti TNFalpha therapy on arterial diameter and wall shear stress and HDL cholesterol. *Atherosclerosis* **177**, 113–118 (2004).
32. Laurent, S. *et al.* Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* **37**, 1236–1241 (2001).
33. Wilkinson, I. B. *et al.* Pulse-wave analysis: clinical evaluation of a noninvasive, widely applicable method for assessing endothelial function. *Arterioscler. Thromb. Vasc. Biol.* **22**, 147–152 (2002).
34. Weber, T. *et al.* Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation* **109**, 184–189 (2004).
35. Mäki-Petäjä, K. M. *et al.* Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-alpha therapy. *Circulation* **114**, 1185–1192 (2006).
36. Avalos, I. *et al.* Increased augmentation index in rheumatoid arthritis and its relationship to coronary artery atherosclerosis. *J. Rheumatol.* **34**, 2388–2394 (2007).
37. Van Doornum, S., McColl, G. & Wicks, I. P. Tumour necrosis factor antagonists improve disease activity but not arterial stiffness in rheumatoid arthritis. *Rheumatology (Oxford)* **44**, 1428–1432 (2005).
38. Van Doornum, S., McColl, G. & Wicks, I. P. Atorvastatin reduces arterial stiffness in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* **63**, 1571–1575 (2004).
39. Jonsson, S. W. *et al.* Increased prevalence of atherosclerosis in patients with medium term rheumatoid arthritis. *J. Rheumatol.* **28**, 2597–2602 (2001).
40. Gonzalez-Juanatey, C. *et al.* High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. *Arthritis Rheum.* **57**, 1074–1780 (2007).
41. Gonzalez-Juanatey, C., Llorca, J., Garcia-Porrua, C., Martin, J. & Gonzalez-Gay, M. A. Effect of anti-tumor necrosis factor alpha therapy on the progression of subclinical atherosclerosis in severe rheumatoid arthritis. *Arthritis Rheum.* **55**, 150–153 (2006).
42. Del Porto, F. *et al.* Response to anti-tumour necrosis factor alpha blockade is associated with reduction of carotid intima–media thickness in patients with active rheumatoid arthritis. *Rheumatology (Oxford)* **46**, 1111–1115 (2007).
43. Hotamisligil, G. S., Arner, P., Caro, J. F., Atkinson, R. L. & Spiegelman, B. M. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J. Clin. Invest.* **95**, 2409–2415 (1995).
44. Dandona, P. *et al.* Tumor necrosis factor-alpha in sera of obese patients: fall with weight loss. *J. Clin. Endocrinol. Metab.* **83**, 2907–2910 (1998).
45. Gonzalez-Gay, M. A. *et al.* Influence of anti-TNF-alpha infliximab therapy on adhesion molecules associated with atherogenesis in patients with rheumatoid arthritis. *Clin. Exp. Rheumatol.* **24**, 373–379 (2006).
46. Yazdani-Biuki, B. *et al.* Improvement of insulin sensitivity in insulin resistant subjects during prolonged treatment with the anti-TNF-alpha antibody infliximab. *Eur. J. Clin. Invest.* **34**, 641–642 (2004).
47. Kiortsis, D. N., Mavridis, A. K., Vasakos, S., Nikas, S. N. & Drosos, A. A. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. *Ann. Rheum. Dis.* **64**, 765–766 (2005).
48. Sarwar, N., Sattar, N., Gudnason, V. & Danesh, J. Circulating concentrations of insulin markers and coronary heart disease: a quantitative review of 19 Western prospective studies. *Eur. Heart J.* **28**, 2491–2497 (2007).
49. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* **91** (**Suppl. 5**), v1–v52 (2005).
50. Allanore, Y., Kahan, A., Sellam, J., Ekindjian, O. G. & Borderie, D. Effects of repeated infliximab therapy on serum lipid profile in patients with refractory rheumatoid arthritis. *Clin. Chim. Acta* **365**, 143–148 (2006).
51. Vis, M. *et al.* Short term effects of infliximab on the lipid profile in patients with rheumatoid arthritis. *J. Rheumatol.* **32**, 252–255 (2005).
52. Popa, C. *et al.* Influence of anti-tumour necrosis factor therapy on cardiovascular risk factors in patients with active rheumatoid arthritis. *Ann. Rheum. Dis.* **64**, 303–305 (2005).
53. Sattar, N. *et al.* Effects of tumor necrosis factor blockade on cardiovascular risk factors in psoriatic arthritis: a double-blind, placebo-controlled study. *Arthritis Rheum.* **56**, 831–839 (2007).
54. Peters, M. J. *et al.* Changes in lipid profile during infliximab and corticosteroid treatment in rheumatoid arthritis. *Ann. Rheum. Dis.* **66**, 958–961 (2007).
55. Popa, C. *et al.* Modulation of lipoprotein plasma concentrations during long-term anti-TNF therapy in patients with active rheumatoid arthritis. *Ann. Rheum. Dis.* **66**, 1503–1507 (2007).
56. Rossner, S. & Lofmark, C. Dyslipoproteinaemia in patients with active, chronic polyarthritis. A study on serum lipoproteins and triglyceride clearance (intravenous fat tolerance test). *Atherosclerosis* **28**, 41–52 (1977).
57. Vermont, C. L. *et al.* Serum lipids and disease severity in children with severe meningococcal sepsis. *Crit. Care Med.* **33**, 1610–1615 (2005).
58. Alexopoulos, C. G., Pournaras, S., Vaslamatzis, M., Avgerinos, A. & Raptis, S. Changes in serum lipids and lipoproteins in cancer patients during chemotherapy. *Cancer Chemother. Pharmacol.* **30**, 412–416 (1992).
59. Akgun, S., Ertel, N. H., Mosenthal, A. & Oser, W. Postsurgical reduction of serum lipoproteins: interleukin-6 and the acute-phase response. *J. Lab. Clin. Med.* **131**, 103–108 (1998).
60. Popa, C. *et al.* Anti-inflammatory therapy with TNFα inhibitors improves HDL-cholesterol anti-oxidative capacity in rheumatoid arthritis patients. *Ann. Rheum. Dis.* doi:10.1136/ard.2008.092171 (2008).
61. Jick, S. S., Choi, H., Li, L., McInnes, I. B. & Sattar, N. Hyperlipidaemia, statin use and the risk of developing rheumatoid arthritis. *Ann. Rheum. Dis.* **68**, 546–551 (2008).
62. Listing, J. *et al.* Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? *Arthritis Rheum.* **58**, 667–677 (2008).
63. Jacobsson, L. T. *et al.* Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J. Rheumatol.* **32**, 1213–1218 (2005).
64. Dixon, W. G. *et al.* Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum.* **56**, 2905–2912 (2007).
65. Dixon, W. G. *et al.* Rates of myocardial infarction and cerebrovascular accident are reduced in patients with rheumatoid arthritis treated with anti-TNF therapy compared to those treated with traditional DMARDS: results from the BSR biologics register. *Ann. Rheum. Dis.* **65** (**Suppl. II**), 109 (2006).
66. Mann, D. L. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. *Circ. Res.* **91**, 988–998 (2002).
67. Levine, B., Kalman, J., Mayer, L., Fillit, H. M. & Packer, M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N. Engl. J. Med.* **323**, 236–241 (1990).
68. Chung, E. S. *et al.* Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation* **107**, 3133–3140 (2003).
69. Mann, D. L. *et al.* Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* **109**, 1594–1602 (2004).
70. Kwon, H. J., Coté, T. R., Cuffe, M. S., Kramer, J. M. & Braun, M. M. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann. Intern. Med.* **138**, 807–811 (2003).
71. Nicola, P. J. *et al.* The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. *Arthritis Rheum.* **52**, 412–420 (2005).
72. Smolen, J. S. *et al.* Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* **371**, 987–997 (2008).
73. Choy, E. & Sattar, N. Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. *Ann. Rheum. Dis.* **68**, 460–469 (2009).
74. Gonzalez-Juanatey, C. *et al.* Short-term improvement of endothelial function in rituximab-treated rheumatoid arthritis patients refractory to tumor necrosis factor alpha blocker therapy. *Arthritis Rheum.* **59**, 1821–1824 (2008).

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Editorial

Non-steroidal anti-inflammatory drugs—changes in prescribing may be warranted

Non-steroidal anti-inflammatory drugs (NSAIDs) are among one of the most frequently prescribed classes of drugs. Both their benefits and harms arise due to inhibition of cycloxygenase (COX) of which there are two isoenzymes, COX 1 and 2. Both COX isoenzymes have a hydrophobic tunnel, through which the substrate accesses the active site. The tunnel is larger in the COX 2 isoenzyme with a side pocket, a property exploited in the development of specific COX 2 inhibitors [1]. The premise of the initial, COX 2 hypothesis was that the gastrointestinal side effects arose due to inhibition of COX 1 whereas their anti-inflammatory or analgesic properties were COX 2 mediated. Although now appreciated to be rather naïve, the superiority of the selective COX 2 inhibitors in preventing gastro-duodenal mucosal ulceration over the non-selective NSAIDs is striking [2, 3].

There has been continuing scientific and media attention on reports that selective COX 2 inhibitors increase the risk of cardiovascular events. In an early study of major gastrointestinal events, an unexpected 5-fold increase in the risk of acute myocardial infarction (AMI) with rofecoxib was observed when compared with naproxen [4]. At the time, many suggested and aggressively pursued the hypothesis that the increased frequency of events was a spurious observation not due to any prothrombotic effects of rofecoxib, but the cardioprotective properties of naproxen. However, subsequent placebo-controlled studies of both rofecoxib, and celecoxib in chemoprevention also reported an approximate 2-fold increase in cardiovascular events with both drugs [5, 6].

More recently, attention has turned to the effects of the non-selective NSAIDs. As aspirin confers its cardiovascular benefits by inhibiting COX 1 [7], received wisdom has never considered the possibility that the non-selective NSAIDs could increase the risk of cardiovascular events. However, in February 2005, the Food and Drugs Administration (FDA) decided to advise that the risk of cardiovascular events for both selective COX 2 and non-selective NSAIDs is similar and has taken the step to categorize this as a class effect [8]. In the US, all COX 2 selective and non-selective NSAIDs now carry a black-boxed warning on the package insert advising patients of the potential increased cardiovascular risk [9]. The European Agency for the Evaluation of Medicine Products (EMEA) [10] and the Medicines and Healthcare Products Regulatory Agency (MRHA) [11] have, however, been much more reassuring with regard to non-selective NSAIDs and advised that 'the data are insufficient to warrant changes in current prescribing'.

The association between increased AMI risk and non-selective NSAIDs has been evaluated predominantly in observational studies [12–28]. These were primarily based on data from large population and hospital databases that recorded the prevalence of NSAID use combined with confirmed AMI diagnosis. While most studies also accounted for the presence of other risk factors, confounders and use of aspirin, few recorded the indication and duration of NSAID use [15, 16, 18]. Overall, a general direction of effect has been reported from the observational studies—with the exception of one study [21], which reported no effect between non-selective NSAID use and AMI, all studies showed a similar trend of increased risk of AMI compared with remote and non-use, ranging from relative risk of 1.00 (95% CI: 0.73–1.37) [21] to 1.47 (95% CI: 1.00–2.16) [22]. Although the size of the overall relative risk appears small, however, due to the large number of patients prescribed NSAIDs, the absolute risk may be considerable. In addition, these studies have presented data that suggested a differential risk between individual NSAID such as diclofenac, naproxen and ibuprofen, but there is insufficient evidence to conclude whether this truly represents a class effect.

The main concern in the context of these studies is whether the small effect observed is a real one or due to unknown or unmeasured confounding factors, a limitation that is inherent to all observational studies. However, such studies may be the only feasible method to determine the potential harms of drugs if the effects are small.

It has been advocated that the only method to resolve the issue would be to undertake a large randomized-control trial of non-selective NSAIDs *vs* placebo [29]. However, it is unlikely that such trial would ever be funded, and it would be unethical to randomize patients to an intervention that may be potentially harmful.

Kearney *et al.* [30] have undertaken a meta-analysis of data of vascular events from randomized-controlled trials of selective COX 2 inhibitors. They found that in all studies selective COX 2 inhibitors increased the risk of vascular events, mainly AMI by 42% (rate ratio 1.42; 95% CI: 1.13–1.78). Trials that compared a COX 2 inhibitor with a traditional NSAID ($n = 91$ trials) showed no significant difference in the risk of vascular events (rate ratio 1.16; 95% CI: 0.97–1.38). There were no significant differences whether all non-selective NSAIDs were considered together, in combination, or alone when compared with COX 2 inhibitors. However, a comparison of non-selective NSAIDs with placebo showed differences between NSAIDs—naproxen was associated with the lowest risk (0.92; 95% CI: 0.67–1.21), but there were insufficient data to show a cardioprotective effect; whereas the rate ratios for ibuprofen and diclofenac were 1.51 (95% CI: 0.96–2.37) and 1.63 (95% CI: 1.12–2.37), respectively. This study thus confirms the findings of the epidemiological studies, but the number of cardiovascular events were small, a limitation acknowledged by the investigators. Furthermore, none of the comparative studies of COX 2 inhibitors with non-selective studies were conducted in patients with high cardiovascular risk or specifically powered to evaluate cardiovascular events.

The MEDAL programme and PRECISION studies are pharmaceutical industry sponsored trials designed to address these concerns. The MEDAL programme consists of three studies (EDGE, EDGE II and MEDAL), and is a non-inferiority comparison of cardiovascular events between etoricoxib and diclofenac [31]. The EDGE studies where originally designed to compare the gastrointestinal tolerability of etoricoxib compared with diclofenac in osteoarthritis and rheumatoid arthritis, whereas the MEDAL study is specifically designed to compare cardiovascular events in 17 804 osteoarthritis and 5700 rheumatoid arthritis patients treated with either etoricoxib or diclofenac. All three studies will continue until the total number of confirmed thrombotic reaches 635 with at least 430 in the MEDAL study. The PRECISION study is a multi-centre comparative study

of celecoxib, diclofenac or ibuprofen coordinated by the Cleveland Clinic which is to report in 4 yrs time [32].

Common to both non-selective NSAIDs and COX 2 inhibitors is the adverse event of hypertension [33, 34]. Most NSAIDs raise blood pressure by approximately 3–5 mmHg [34]. Even such a modest rise will result in a significantly increased frequency of cardiovascular events; a 3 mmHg rise in systolic blood pressure increases the frequency of congestive cardiac failure by 10–20%, increases the risk of stroke up to 20% and angina by 12% [35]. It has also been predicted that a 3 mmHg in blood pressure in rheumatoid arthritis patients in the US will result in an additional 21 390 ischaemic heart disease and stroke events [36]; when extrapolated to the UK rheumatoid arthritis population, this is equivalent to 2058 potentially avoidable fatal events.

The current evidence strongly suggests that the risk for cardiovascular events to be similar for both non-selective NSAIDs and COX 2 inhibitors. The potential size of the problem is substantial. Physicians should reconsider their prescription of non-selective NSAIDs in line with those advocated by the FDA. Any other advice on current prescribing is unwarranted.

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References

1. Kurumbail RG, Stevens AM, Gierse JK *et al*. Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents. Nature 1996;384:644–8.
2. Seibert K, Masferrer J, Zhang Y *et al*. Mediation of inflammation by cyclooxygenase-2. Agents Actions (Suppl) 1995;46:41–50.
3. Garner S, Fidan D, Frankish R *et al*. Celecoxib for rheumatoid arthritis. Cochrane Database Syst Rev 2002;4:CD003831.
4. Bombardier C, Laine L, Reicin A *et al*. VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis – VIGOR Study Group. N Engl J Med 2000;343:1520–8.
5. Bresalier RS, Sandler RS, Quan H *et al*. Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352:1092–102.
6. Solomon SD, McMurray JJ, Pfeffer MA *et al*. Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352:1071–80.
7. Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Drug therapy: low dose aspirin for prevention of atherothrombosis. N Engl J Med 2005;353:2373–83.
8. TMT Review of cardiovascular safety of Celebrex. January 2005. Accessed 23 August 2006. Page 8 of http://www.fda.gov/ohrms/dockets/dockets/04n0559/04N-0559_emc-00002-01.pdf
9. Decision Memo: Analysis and recommendations for Agency action: Cox 2 selective and non-selective NSAIDs. Accessed 23 August 2006. http://www.fda.gov/cder/drug/infopage/cox2/NSAIDdecisionmemo.pdf
10. EMEA press release on non-selective NSAIDS, 2nd August 2005. Accessed 23 August 2006. http://www.emea.eu.int/pdfs/human/press/pr/24732305en.pdf
11. MHRA release: "Cardiovascular safety of NSAIDs – review of the evidence". Accessed 23 August 2006. http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dID=1428&noSaveAs=0&Rendition=WEB
12. Kimmel SE, Berlin JA, Reilly M *et al*. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. Ann Intern Med 2005;142:157–64.
13. Kimmel SE, Berlin JA, Reilly M *et al*. The effects of non-selective non-aspirin non-steroidal anti-inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. J Am Coll Cardiol 2004;43:985–90.
14. Jick SS. The risk of gastrointestinal bleed, myocardial infarction, and newly diagnosed hypertension in users of meloxicam, diclofenac, naproxen and piroxicam. Pharmacotherapy 2000;20:741–4.
15. Watson DJ, Rhodes T, Cai B, Guess HA. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. Arch Intern Med 2002;162:1105–10.
16. Garcia Rodriguez LA, Varas C, Patrono C. Differential effects of aspirin and non-aspirin nonsteroidal antiinflammatory drugs in the primary prevention of myocardial infarction in postmenopausal women. Epidemiology 2000;11:382–7.
17. Fischer L, Schlienger RG, Matter CM, Jick H, Meir CR. Current use of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction. Pharmacotherapy 2005;25:503–10.
18. Garcia Rodriguez LA, Varas-Lorenzo C, Maguire A, Gonzalez-Perez A. Non steroidal anti-inflammatory drugs and the risk of myocardial infarction in the general population. Circulation 2004;109:3000–6.
19. Graham DJ, Campen D, Hui R *et al*. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet 2005;65:475–81.
20. Johnsen SP, Larsson H, Tarone RE *et al*. Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs: a population-based case-control study. Arch Intern Med 2005;165:978–84.
21. Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults. Ann Intern Med 2005;142:481–9.
22. Mamdani M, Rochon P, Juurlink DN *et al*. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. Arch Intern Med 2003;163:481–6.
23. Ray W, Stein MC, Daugherty JR, Hall K, Arbogast PG, Griffin MR. Cox-2 selective non steroidal anti-inflammatory drugs and risk of coronary heart disease. Lancet 2002;360:1071–3.
24. Ray W, Stein MC, Hall K, Daugherty JR, Griffin MR. Non steroidal anti-inflammatory drugs and risk of serious coronary heart disease; an observational cohort. Lancet 2002;359:118–23.
25. Rhame E, Pilote L, LeLorier J. Association between naproxen use and protection against acute myocardial infarction. Arch Intern Med 2002;162:1111–5.
26. Schlienger RG, Jick H, Meier CR. Use of non steroidal anti-inflammatory drugs and the risk of first acute myocardial infarction. Br J Clin Pharmacol 2002;54:327–32.
27. Solomon DH, Glynn RJ, Levin R, Avorn J. Nonsteroidal anti-inflammatory drug use and acute myocardial infarction. Arch Intern Med 2002;162:1099–104.
28. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. Br Med J 2005;330:1366.
29. Juni P, Reichenbach S, Egger M. COX-2 inhibitors, traditional NSAIDs, and the heart. Br Med J 2005;330:1342–3.
30. Kearney PM, Baignent C, Godwin J, Halls H, Emerson JR. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of

atherothrombosis? Meta-analysis of randomised trials. Br Med J 2006;332:1302–8.
31. Cannon CP, Curtis SP, Bolognese JA, Laine L – for the MEDAL Steering Committee. Clinical trial design and patient demographics of the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Study Program: cardiovascular outcomes with etoricoxib versus diclofenac in patients with osteoarthritis and rheumatoid arthritis. Am Heart J 2006;152:237–45.
32. Cleveland Clinic website, PRECISION study. Accessed 23 August 2006. http://www.clevelandclinic.org/heartcenter/pub/news/archive/2005/painrelief12_13.asp
33. Aisen PS, Schafer K, Grundman M *et al*. NSAIDs and hypertension. Arch Int Med 2003;163:1115.
34. Johnson AG, Nguyen TV, Day RO. Do non-steroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994;121:289–300.
35. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin *vs* chlorthalidone. JAMA 2000;283:1967–75.
36. Singh G, Miller JD, Huse DM *et al*. Consequences of increased systolic blood pressure in patients with osteoarthritis and rheumatoid arthritis. J Rheumatol 2003;30:714–9.