HEART FAILURE AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE: COMMON PARTNERS, COMMON PROBLEMS

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Abbreviations

ACEI – angiotensin converting enzyme inhibitor
BNP – B-type natriuretic peptide
CHARM – Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity programme
CI – confidence interval
CMR – cardiac magnetic resonance imaging
COPD – chronic obstructive pulmonary disease
CRF – case report form
CRP – C-reactive protein
CRQ – Chronic Respiratory Questionnaire
CV – cardiovascular
DLCO – diffusing capacity of the lung for carbon monoxide
ECG – electrocardiogram
FEV_1 – forced expiratory volume in 1 second
FVC – forced vital capacity
GOLD – Global Initiative for Chronic Obstructive Lung Disease
GP – general practitioner
HF – heart failure
HF-PEF – heart failure with preserved ejection fraction
HR – hazard ratio
KCO – carbon monoxide transfer coefficient
LVEF – left ventricular ejection fraction
LVSD – left ventricular systolic dysfunction
MI – myocardial infarction
MLHFQ – Minnesota Living with Heart Failure Questionnaire
NYHA – New York Heart Association
OR – odds ratio
$PaCO_2$ – partial pressure of carbon dioxide
PaO_2 – partial pressure of oxygen
PEF – peak expiratory flow
QOF – Quality and Outcomes Framework
REC – research ethics committee
RR – risk ratio
RV – residual volume
SAE – serious adverse event
SaO_2 – oxygen saturation
SF-36 – Short Form 36
SUSARS – suspected unexpected serious adverse reactions
TLC – total lung capacity
TORCH – Towards a Revolution in COPD Health trial
Val-HeFT – Valsartan Heart Failure Trial
VALIANT – Valsartan in Acute Myocardial Infarction Trial

Summary

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are common partners with common problems. Both are chronic systemic disorders incurring significant morbidity and mortality. Although around one third of patients with HF have concurrent COPD,[1] remarkably few reports have addressed this often ignored combination. The systematic review presented within this thesis defines the diagnostic challenges, prevalence and prognostic implications of HF with coexistent COPD. I then critically appraise the twin controversies of β-blockade in COPD and β-agonists in HF. The two are inextricably linked, each therapy exerting the reverse pharmacologic activity of the other. The evidence for symptomatic or prognostic benefit from either therapy is limited, and in the case of β-agonists adverse consequences appear more likely.

A Cochrane meta-analysis concluded that long term cardioselective β-blockade is safe and well tolerated in patients with moderate to severe or reversible COPD.[2] Although often cited,[3] these conclusions are simply not true. Of the 20 randomised controlled trials included in the meta-analysis, 11 involved single doses and only one lasted longer than a month. The 9 'long term' studies (defined as more than a single treatment dose) involved 147 young, predominantly male patients with moderate airways obstruction (mean forced expiratory volume in 1 second (FEV_1) 1.8 litres). The effect on health status has never been assessed in any cohort with COPD. The long term impact of β-blockade on pulmonary function, symptoms and quality of life is therefore largely unknown. Most importantly, no study has included patients with HF.

I randomised 27 patients with HF and coexistent moderate or severe COPD to receive bisoprolol or placebo, titrated to maximum tolerated dose over 4 months. Patients were elderly and predominantly male. Cardiovascular comorbidity, smoking history and pulmonary function were similar in each group (mean FEV_1 1.37L vs 1.26L). There were several key findings. A reduction in FEV_1 occurred after 4 months following treatment with bisoprolol compared with placebo (–70 ml vs +120 ml, p=0.01). Reversibility following inhaled β_2-agonist and static lung volumes were not impaired by bisoprolol. All measures of health status exhibited a consistent non-significant improvement, including the Short Form 36 physical and mental component scores, Minnesota Living with Heart Failure Questionnaire, and Chronic Respiratory Questionnaire. The mean number of COPD exacerbations was similar in the bisoprolol and placebo groups. Although recruitment was limited, the results pose crucial questions and provide direction for larger randomised controlled trials.

I analysed cross-sectional data from 61 primary care practices (377,439 patients) participating in the Scottish Continuous Morbidity Recording scheme. The prevalence of COPD in patients with HF increased year on year from 19.8% in 1999 to 23.8% in 2004. These changes may previously have been attributed to an ageing population or increasing age of presentation. However, the trend remained significant after age standardisation. A clear socioeconomic gradient was observed, with prevalence greatest in the most deprived. Consultation rates for HF or COPD in those with both conditions were greater than disease specific contact rates in patients with either condition alone. Cardiovascular comorbidity was similar in HF patients with and without COPD, despite differences in smoking history (respectively 76% vs 47%, p<0.001). This is concerning and suggests that common cardiovascular

conditions are being under diagnosed (and likely under treated) in patients with HF and COPD.

Although overall β-blocker prescribing increased over time, the adjusted odds of β-blocker prescription in patients with COPD was low (odds ratio 0.30 [95% CI 0.28–0.32], p<0.001). Whether the gap between patients with and without COPD is improving was previously unknown. Despite the overall improvement in beta-blocker prescribing, the relative difference in prescribing between those with and without COPD remained unchanged. By 2004, only 18% of individuals with HF and COPD were prescribed β-blockers.

COPD is consistently an independent predictor of death and HF hospitalisation in patients with HF. However, the causes of increased mortality were unclear. I examined the relationship between COPD and cardiovascular outcomes in patients with myocardial infarction (MI) complicated by heart failure, left ventricular systolic dysfunction (LVSD), or both enrolled in the Valsartan in Acute Myocardial Infarction (VALIANT) trial. COPD was an independent predictor of mortality, largely due to increased non-cardiovascular (HR 1.86 [1.43–2.42]) and sudden death (HR 1.26 [1.03–1.53]). However, after multivariate adjustment COPD was not an independent predictor of atherosclerotic events (MI or stroke: HR 0.98 [0.77–1.23]). This is an important finding, as atherosclerotic consequences of chronic systemic inflammation in COPD have been postulated. These appear of limited clinical significance, at least during intermediate follow-up.

Part of the adverse risk associated with COPD may be attributable to bronchodilators. The prognosis of patients with HF prescribed bronchodilators is however ill defined. I examined the prognostic implications of bronchodilator use in

patients with HF enrolled in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) programme. The diversity and magnitude of adverse outcomes associated with bronchodilator therapy was surprising. Bronchodilator use was associated with increased all cause mortality (HR 1.26 [1.09–1.45]), cardiovascular death (HR 1.21 [1.03-1.42]), death due to HF progression (HR 1.40 [1.07-1.82]) and HF hospitalisation (HR 1.49 [1.29-1.72]). Although association is not causation, it is possible that bronchodilators compound maladaptive remodeling and further depress myocardial function.

Finally, β-blockers were independently associated with better survival in both VALIANT and CHARM. No significant interaction was observed between either COPD or bronchodilators and β-blockade with respect to mortality. Furthermore, β-blocker use was not associated adversely with any pre-specified outcome in patients with COPD or those prescribed bronchodilators, including non-cardiovascular mortality. Although recruitment bias and the absence of spirometry limit inference to patients with severe or reversible airflow obstruction, the results should encourage β-blockade in patients with COPD.

In summary, the studies presented in this thesis extend our understanding of HF with concurrent COPD. Only large randomised controlled trials will solve the quandary of β-blockers and β-agonists. Justification for these trials evolves from observational data and smaller prospective studies such as my own. In the meantime, I hope the evidence presented will stimulate physicians to re-evaluate the management of patients with HF and COPD.

Chapter 1

Introduction

1.1 The questions that interest physicians

Heart failure and chronic obstructive pulmonary disease are global epidemics, each affecting in excess of ten million patients.[4,5] Both conditions incur significant morbidity and mortality, and present major challenges to healthcare providers.[5] Around one third of patients with HF have concurrent COPD.[1] Few reports have addressed this often ignored combination, and fewer still the simple questions of interest to physicians. What are the pitfalls of diagnosing HF in patients with COPD, and vice-versa? How frequent a comorbidity is COPD? What are the clinical consequences of both conditions co-existing?

The cornerstones of therapy are β-blockers and β-agonists respectively. The short and long term effects of β-blockade are diametrically opposed: acute negative inotropy precedes improved left ventricular systolic function. β-blockers confer protection from chronically elevated catecholamines and lead to up-regulation of β-receptors. Reverse remodeling follows. β-agonists exert the reverse pharmacologic effects of β-blockers. Exposure induces down-regulation and desensitization of β-receptors.[6] However, whether acute positive inotropy gives way to longer term left ventricular systolic dysfunction is uncertain. Further questions arise. Does 'severe' or 'reversible' airflow obstruction preclude β_1-selective blockade? Is bronchoconstriction lessened by using a β-blocker with α_1-antagonist activity? Do β-blockers improve the prognosis of patients with both conditions? How safe are oral and inhaled β-agonists in patients with HF?

This introduction examines the diagnostic problems posed by the two conditions, before reviewing the prevalence and prognostic implications of COPD in

patients with HF. Finally, the controversial issues of β-blockers and β-agonists in patients with HF and COPD are critically appraised.

1.2 Problems diagnosing HF in patients with COPD

1.2.1 Clinical features

HF is a complex syndrome without a simple objective definition. Diagnosis requires both typical clinical features and objective evidence of cardiac dysfunction.[4] Pulmonary disease may produce or obscure every symptom and sign defined by Framingham criteria.[7] Exertional breathlessness, nocturnal cough and paroxysmal nocturnal dyspnoea are common to both conditions. No qualitative features of dyspnoea are unique to HF.[8] Stigmata of right ventricular failure may also be misleading, including jugular venous distention, ankle oedema and hepatomegaly. Lung hyperinflation with hepatic displacement mimics the latter, while hindering palpation of cardiomegaly and auscultation of rales or a third heart sound. The difficulty in differentiating between HF and COPD symptoms and signs is illustrated in a single cohort study comparing the Framingham and Cardiovascular Health Study criteria for HF. The prevalence of concurrent COPD was twice as great in patients fulfilling only Framingham as opposed to only Cardiovascular Health Study criteria (13% vs 6%).[9]

1.2.2 Radiology

Radiological evidence of HF is likewise influenced by the presence of COPD.[10,11] Chest hyperinflation spuriously reduces the cardiothoracic ratio.

Pulmonary vascular remodeling and radiolucent lung fields mask the typical alveolar shadowing of pulmonary oedema.[11,12] Asymmetric, regional, and reticular patterns of pulmonary oedema are commonplace in those with concurrent COPD.[10,11,13] Emphysematous vascular bed loss causes upper lobe venous diversion, mimicking HF.[13] Isolated right heart failure is also said to cause pleural effusions through impaired pleural lymphatic drainage secondary to elevated systemic venous pressure.[14] However, in clinical practice pleural effusions are rarely due to right heart failure alone.[15,16]

1.2.3 Echocardiography

Transthoracic echocardiography may be impeded by poor acoustic windows caused by the pathological changes associated with COPD.[17] Inadequate visualisation may relate to air trapping. In a recent primary care study echocardiographic images were unsatisfactory in 10.4% of patients with COPD.[18] This proportion increases to 35% in patients with severe COPD,[19] and 50% in those with very severe airflow obstruction.[20] Although studies have assessed contrast echocardiography in patients with poor endocardial definition, those with pulmonary disease were often excluded.[21,22] In lung transplant candidates, Doppler estimation of pulmonary artery pressure was less frequently possible in patients with a residual volume exceeding 150% predicted (40% versus 56%, p=0.007).[23] Studies would be welcome comparing the accuracy of left ventricular ejection fraction (LVEF) measured by contrast echocardiography against cardiac magnetic resonance imaging (CMR) in patients with COPD.

1.2.4 Cardiac magnetic resonance imaging

CMR is the accepted reference standard for measuring LV volumes and ejection fraction.[24] Results are accurate, reproducible and extensively validated.[24,25] CMR allows precise quantification of right ventricular volumes, function and transvalvular flow, while avoiding ionising radiation.[26] Tissue characterisation additionally identifies myocardial fibrosis which may predict risk of arrhythmias.[27] Professional imaging societies recommend CMR to evaluate LV function in heart failure patients with technically limited echocardiogram images.[28]

1.2.5 Natriuretic peptides

Both B-type natriuretic peptide (BNP) and N-terminal pro-BNP are useful for excluding HF in subjects with acute dyspnoea.[29-31] The diagnostic accuracy of BNP in patients with concurrent COPD is less certain. Subgroup analysis of 417 patients with COPD or asthma in the Breathing Not Properly study reported a mean BNP for those with and without HF of 587 ± 426 pg/ml and 109 ± 221 pg/ml respectively ($p<0.0001$).[32] In a Californian study of 321 patients presenting with acute dyspnoea, mean BNP was significantly higher in patients with HF compared to those with COPD (759 ± 798 pg/ml vs 54 ± 71 pg/ml, $p<0.001$).[33] Both studies have two major limitations. Firstly, the diagnosis of HF was adjudicated retrospectively by two cardiologists based on clinical criteria and subsequent investigations; in the Breathing Not Properly subgroup only 29% of patients had echocardiography.[32] Secondly, right heart failure from cor pulmonale was possibly misdiagnosed or even specifically classified as HF.[33] This falsely magnifies the apparent accuracy of BNP

while neglecting the question of interest to clinicians, for whom diagnosing HF due to left ventricular dysfunction is paramount in guiding future therapy.

Plasma BNP is elevated in both primary pulmonary hypertension and right heart failure secondary to chronic respiratory disease.[34-37] Levels of BNP correlate with pulmonary artery pressure and independently predict mortality.[34-37] However, few studies have assessed BNP specifically in patients with COPD.[36,38] Only one has examined the ability to identify HF in these patients.[39] Four natriuretic peptide assays produced comparable results in 200 stable elderly patients with a clinical diagnosis of COPD. Each test excluded HF with reasonable accuracy (all negative predictive values above 0.85). However, the positive predictive value and overall diagnostic accuracy was lower than observed in patients with acute dyspnoea.[30,31] The explanation is twofold. Stable patients exhibit lower BNP levels than those with acute volume overload and raised intracardiac pressures. Secondly, BNP levels are increased in patients with COPD.[36,39] Both factors lessen the diagnostic accuracy in these patients. The BNP Consensus Panel guidelines state that cor pulmonale is associated with an intermediate elevation of BNP, typically ranging from 100 to 500 pg/ml.[29] Levels below 100 pg/ml and above 500 pg/ml have high negative and positive predictive values respectively for HF. Between these thresholds a Bayesian approach is warranted, using BNP to corroborate the clinical evaluation.

1.2.6 Heart failure with preserved ejection fraction

Defining and identifying HF with preserved ejection fraction (HF-PEF) is controversial and problematic in any population. These difficulties are magnified in patients with COPD. BNP levels are moderately elevated in both HF-PEF and cor

pulmonale.[40-42] One small study compared 17 patients with COPD against 9 patients with HF-PEF, defined by clinical and radiological pulmonary oedema responding to treatment, sinus rhythm and preserved LV ejection fraction. BNP levels were significantly higher in those with HF-PEF (224 vs 14 pg/ml, $p<0.0001$).[38] However, BNP was below 100 pg/ml in 4 of the 9 patients with HF-PEF, while few patients with COPD had significant pulmonary hypertension (mean systolic pulmonary artery pressure was 36 mmHg). More robust studies are required to determine the diagnostic accuracy of BNP for HF in patients with COPD and varying levels of pulmonary hypertension.

1.3 Problems diagnosing COPD in patients with HF

1.3.1 Definition of obstruction and restriction

Patients with HF exhibit both obstructive and restrictive ventilatory defects, which may compound or conceal the characteristic airflow limitation of COPD. Spirometry defines three standard indices: forced expiratory volume in one second (FEV_1); forced vital capacity (FVC), the total volume delivered during forced expiration from a maximum inspiration; FEV_1/FVC ratio, the proportion of the total volume expired in the first second.[43] Obstruction is defined by a reduced FEV_1/FVC ratio below 70% in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and American Thoracic Society / European Respiratory Society guidelines.[5,44] Restriction is characterised by reduced lung volumes. Both FEV_1 and FVC are decreased with a normal or raised FEV_1/FVC ratio. Since this pattern also

occurs in severe obstruction with air trapping, the diagnosis of restriction additionally requires detection of reduced total lung capacity by plethysmography.[43]

1.3.2 Obstructive pulmonary function tests

Airflow obstruction is common in patients with decompensated HF,[45,46] contrasting with restrictive defects when HF is stable. Interstitial and alveolar oedema cause compression and obstruction of the airways, compounded by bronchial hyperresponsiveness.[47,48] Both misdiagnosis and overestimation of COPD severity may result. With diuresis, mean FEV_1 improves by up to 35% and often returns to normal.[45-47] Pulmonary function tests are therefore most informative when patients are clinically euvolaemic.

A mild obstructive ventilatory pattern may be observed even when not fluid overloaded. A comparison dichotomising patients around a peak oxygen consumption of 14 ml/min/kg noted a lower FEV_1/FVC ratio in severe HF (70% vs 75%, p=0.008).[49] The ratio also declines with age in the general population, reaching 70% in those over 75 years of age.[50] COPD may thus be over diagnosed in elderly patients with HF.[51]

1.3.3 Restrictive pulmonary function tests

Restrictive ventilatory defects predominate in patients with stable HF.[52] FEV_1 and FVC were normal or proportionately reduced in a multicentre study of 130 patients.[53] Contributory factors include interstitial fibrosis,[54] respiratory muscle weakness,[49,55,56] cardiomegaly and pulmonary congestion.[57] FEV_1 and FVC may also be proportionately reduced with a normal ratio in patients with severe COPD

and gas trapping. Usually in such cases increased total lung capacity and residual volume help diagnose obstruction.[43] However, restricted lung volumes mask hyperinflation and thus the diagnosis of COPD in patients with concurrent HF.[10]

1.3.4 Performing spirometry

Objective evidence of airflow obstruction is mandatory for diagnosing COPD.[5] Approximately one third of patients labelled with COPD do not fulfil the GOLD criteria (Table 1.1).[39,58] Despite this, many physicians fail to confirm or refute the clinical diagnosis using spirometry. A recent US study revealed significant disparities in confirmatory testing practices.[58] Among 219 patients discharged from a tertiary centre with both HF and COPD, 82% received echocardiography as opposed to 36% pulmonary function testing. This lack of adherence to guidelines must be addressed, as both inhaled therapy and β-blockade are dictated by the degree of airflow obstruction.

Table 1.1 GOLD classification of COPD severity based on post-bronchodilator FEV_1

Stage	FEV_1/FVC	Post-bronchodilator FEV_1 predicted
I: Mild	< 0.70	$FEV_1 \geq 80\%$
II: Moderate	< 0.70	$50\% \leq FEV_1 < 80\%$
III: Severe	< 0.70	$30\% \leq FEV_1 < 50\%$
IV: Very Severe	< 0.70	$FEV_1 < 30\%$ or $FEV_1 < 50\%$ plus chronic respiratory failure

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; Respiratory failure: arterial partial pressure of oxygen (PaO_2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.

1.4 Epidemiology of HF and COPD

1.4.1 Prevalence of COPD in patients with HF

Estimates of COPD prevalence vary according to the population studied, diagnostic criteria applied, measurement tools and surveillance systems.[59] Geographical variations largely relate to differences in population age structure and risk factor exposure, most notably smoking.[5,59] The prevalence of COPD was greater in patients with HF than the general population in the Cardiovascular Health Study (20% vs 13%, p=0.001).[60] This may reflect both clustering of aetiological factors and misdiagnosis. No study has systematically examined pulmonary function in patients with stable HF.[61] How many have severe, reversible, or misdiagnosed airflow obstruction is unknown.

The reported prevalence of COPD ranges from 11% to 52% in North American patients with HF, and from 9% to 41% in European cohorts (Table 1.2). Half the studies originate in the United States. The prevalence of COPD is greater in more recent studies (Table 1.2). Four studies examining trends in HF epidemiology confirm the increasing prevalence.[62-65] This may represent greater awareness of COPD, an ageing population or increasing age at onset of HF. A consistent non-linear relationship is apparent between age and frequency of concurrent COPD in patients with HF.[66-69] The prevalence increases until around 75 years of age, and declines thereafter. Possibly the presence of COPD reduces survival beyond this age. Alternatively, less intensive investigations in the elderly may under-diagnose comorbidity.

Table 1.2 Prevalence of COPD in patients with HF

Reference	Prevalence COPD (%)	Country	Data Collection	n	Population	Data Source
Rich.[70]	11	U.S.	1983-1986	410	HF hospitalisation	Washington University Hospital
Bangdiwala.[71]	15	U.S. Canada	1988-1989	6273	HF hospitalisation	SOLVD Registry
Auerbach.[72]	19	U.S.	1989-1994	1298	HF hospitalisation	SUPPORT Study
Barker.[62]	18	U.S.	1990-1994	393	HF hospitalisation	Kaiser Permanente Centre Health Research
Wang.[73]	12	U.S.	1989-1995	231	HF hospitalisation	Philadelphia Geriatric Centre
Mathew.[74]	19	U.S.	1992-1995	301	Mixed	Cook County Hospital
Harjai.[75]	18	U.S.	1994-1995	434	HF hospitalisation	Ochsner Foundation Hospital
Kitzman.[60]	20	U.S.	1994-1995	425	Outpatient	Cardiovascular Health Study
Vaccarino.[76]	27	U.S.	1994-1995	2445	HF hospitalisation	Connecticut Peer Review Organisation
Gambassi.[67]	19	U.S.	1992-1996	86094	Outpatient	SAGE Database
Polanczyk.[65]	24	U.S.	1994-1996	1896	HF hospitalisation	Massachusetts General Hospital
Baker.[64]	25	U.S.	1991-1997	23505	HF hospitalisation	Cleveland Health Quality Choice Program
Ansari.[77]	26	U.S.	1996-1997	403	Outpatient	Kaiser Permanente Medical Care Program
Braunstein.[78]	26	U.S.	1999	122630	Outpatient	Medicare
Kosiborod.[63]	33	U.S.	1992-1999	3957520	HF hospitalisation	Medicare
Havranek.[68]	33	U.S.	1998-1999	34587	HF hospitalisation	National Heart Failure Project
Rathore.[79]	33	U.S.	1998-1999	30996	HF hospitalisation	National Heart Failure Project
Kamalesh.[80]	52	U.S.	1999-2000	495	Outpatient	Indianapolis Veterans Affairs Medical Centre
Goldberg.[81]	34	U.S.	2000	2445	HF hospitalisation	Worcester Metropolitan Hospitals
Laramee.[82]	22	U.S.	1999-2001	287	HF hospitalisation	Fletcher Allen Medical Centre, Vermont
Rector.[83]	24	U.S.	1999-2003	769	HF hospitalisation	Minneapolis Veterans Affairs Medical Centre
Ezekowitz.[84]	32	Canada	1993-2001	12065	HF hospitalisation	Alberta Health Care Insurance Registry
Lee.[85]	21	Canada	1999-2001	2624	HF hospitalisation	EFFECT Study
Nieminen.[86]	19	Europe	2004-2005	3580	HF hospitalisation	EuroHeart Failure Survey II
Brown.[87]	12	Scotland	1995	27477	HF hospitalisation	Scottish Morbidity Record
Murphy.[88]	15	Scotland	1999-2000	973	Community	Primary Care Records
Newton.[89]	9	England	1998-2001	528	HF hospitalisation	Leicestershire Health Authority
van Jaarsveld.[90]	9	Netherlands	1993-1998	293	Community	Groningen Longitudinal Aging Study
Bouvy.[91]	19	Netherlands	-	152	Mixed	Trial of Pharmacist

						Intervention
van der Wel.[69]	25	Netherlands	1999-2003	269	Community	Nijmegen Practice-Based Research Network
Taubert.[92]	11	Germany	1997-1998	266	HF hospitalisation	Ludwigshafen Heart Failure Registry
Jost.[93]	20	Germany	1995-2004	675	Mixed	Ludwigshafen Heart Failure Registry
Martinez-Selles.[94]	30	Spain	1996	1065	HF hospitalisation	Heart failure Observation of Local Admissions
Di Lenarda.[95]	41	Italy	2000	2127	HF hospitalisation	TEMISTOCLE Study
Senni.[96]	17	Italy	2003	807	Mixed	Italian College of General Practitioners
Macchia.[97]	24	Italy	2003	1020	HF hospitalisation	Northern Italian Local Health Authorities
Tavazzi.[98]	30	Italy	2004	2807	HF hospitalisation	Italian survey on Acute Heart Failure
Siirila-Waris.[99]	13	Finland	2004	620	HF hospitalisation	Finnish Acute Heart Failure Study
Gustafsson.[100]	22	Denmark	1993-1996	5491	HF hospitalisation	DIAMOND-CHF Registry
Galatius.[101]	8	Denmark	1999-2001	283	Community	Frederiksberg University Hospital
Rohde.[102]	21	Brazil	2000-2004	779	HF hospitalisation	Hospital de Clinicas de Porto Alegre
Wright.[103]	19	New Zealand	1996-1997	197	HF hospitalisation	Auckland Heart Failure Management Program
Chong.[104]	12	Malaysia	-	97	HF hospitalisation	Kuala Lumpur General Hospital

COPD, chronic obstructive pulmonary disease; HF, heart failure.

COPD is more common in male compared with female HF patients,[69,76,94,97,100,105] and in urban compared with rural areas.[92] The prevalence is notably lower (by 6–11%) in those managed by cardiologists as opposed to general physicians.[72,77,106,107] Non-cardiac comorbidity is a well recognised barrier to specialty referral.[108] Alternatively, cardiologists perhaps fail to recognise airways disease. In patients with preserved ejection fraction the reported prevalence is generally higher (Table 1.3).[109-119] A degree of misdiagnosis undoubtedly exists.[120] Finally, remarkably few clinical trials report the presence of COPD (Table 1.4). In these, the lower prevalence of 7% to 13% in stable outpatients suggests significant recruitment bias.

Table 1.3 Prevalence of COPD in patients with HF and reduced or preserved left ventricular ejection fraction

Reference	Ejection Fraction	Prevalence COPD (%)	P value Preserved vs Reduced	n	Population	Country
Masoudi.[109]	Preserved	34	p<0.001	6754	HF hospitalisation	U.S.
	Reduced	31		12956		
Ansari.[110]	Preserved	30	p=0.075	147	Community	U.S.
	Reduced	21		191		
Dauterman.[111]	Preserved	33	p=0.32	430	HF hospitalisation	U.S.
	Reduced	29		352		
Gustafsson.[112]	Preserved	26	p<0.001	2218	HF hospitalisation	Denmark
	Reduced	19		3022		
Bursi.[113]	Preserved	38	p=0.06	308	Community	U.S.
	Reduced	30		248		
Bhatia.[114]	Preserved	18	p=0.002	880	HF hospitalisation	Canada
	Reduced	13		1570		
McDermott.[115]	Preserved	21	p=0.80	92	HF hospitalisation	U.S.
	Reduced	19		206		
Liao.[116]	Preserved	21	p=0.02	186	Community	U.S.
	Reduced	11		166		
Ilksoy.[117]	Preserved	41	p=0.72	26	HF hospitalisation	U.S.
	Reduced	36		63		
Kjaergaard.[118]	Preserved	27	p=0.15	96	HF hospitalisation	Denmark
	Reduced	20		276		
Agoston.[119]	Preserved	38	-	121	HF hospitalisation	U.S.
	Reduced	28		327		
Ahmed.[121]	Preserved	24	p=1	238	HF hospitalisation	U.S.
	Reduced	24		200		
Tribouilloy.[122]	Preserved	20	p=0.91	368	HF hospitalisation	France
	Reduced	21		294		
Diller.[123]	Preserved	44	p=NS	54	Community	U.S.
	Reduced	48		82		
Berry.[124]	Preserved	7	p=0.16	130	HF hospitalisation	Scotland
	Reduced	11		315		
Varadarajan.[125] (VA Hospital)	Preserved	4	p<0.0001	963	HF hospitalisation	U.S.
	Reduced	9		1295		

Table 1.4 Prevalence of COPD in HF trials

Reference	n	Prevalence COPD (%)	LVEF (%)	Trial	Population
Parker.[126]	6797	7	≤ 35	SOLVD	Community
Sharma.[127]	3044	9	≤ 40	ELITE II	Community
Staszewsky. [128]	5010	13	< 40	Val-HeFT	Community
Massie.[129]	1587	8	≤ 35	WATCH	Community
Grancelli.[130]	1518	9	Any	DIAL	Community
NETWORK Investigators.[131]	1532	7	-	NETWORK	Mixed
Gheorghiade.[132]	319	10	≤ 40	ACTIV-CHF	HF hospitalisation
Cuffe.[133]	949	23	< 40	OPTIME-CHF	HF hospitalisation

Measurement of ejection fraction inherently changes the estimated prevalence. In the Olmsted County study,[134] 23% of patients with HF had 'restrictive/chronic obstructive pulmonary disease'. However, the prevalence was lower (15%) among those undergoing echocardiographic assessment. An incorrect diagnosis of COPD may be removed once LVSD is confirmed. Additionally, fewer patients with COPD are referred for echocardiography. Across 417 Italian centres, COPD independently predicted failure to assess LV function during hospitalisation (OR 1.25 [95% CI 1.02-1.53]).[95]

1.4.2 Prevalence of HF in patients with COPD

Cigarette smoking, the commonest cause of COPD, is associated with a 50% increased risk of HF.[112,135,136] Two studies have diagnosed HF using standardised criteria in patients with COPD.[32,137] Both examined the prevalence of unrecognised HF, excluding patients with an existing diagnosis. The prevalence of HF was 20.9% in a highly selected cohort with COPD or asthma presenting to the emergency department with acute dyspnoea.[32] However, the diagnosis was adjudicated retrospectively by two cardiologists, with echocardiography performed in only 29% of participants. The prevalence of unrecognised HF was the same (20.5%) in a comprehensive community study of 405 elderly patients with stable COPD.[137] Heart failure was diagnosed by an expert panel following chest radiography, electrocardiography, echocardiography and pulmonary function tests. Not one patient had echocardiographic evidence of isolated right heart failure. This corroborates reports estimating the prevalence of cor pulmonale in COPD to be approximately 0.2%.[138] There is a simple clinical message. Patients with COPD and

suspected heart failure must be considered to have left ventricular dysfunction until proven otherwise.

1.4.3 Prevalence of LVSD in patients with COPD

A recent systematic review identified 18 reports quantifying LVEF among COPD patients, most with small numbers of participants (n=10 to 120).[61] The prevalence of LVSD varied considerably, ranging from 10% to 46% in unselected patients with stable COPD. Studies excluding patients with coronary disease observed a lower prevalence of 0% to 32%.

1.4.4 Relationship between COPD and HF

COPD is characterised by low grade systemic inflammation, which may contribute to the progression of atherosclerosis and adverse cardiovascular events.[139-141] Myocardial dysfunction may ensue. In the NHANES III survey moderate to severe airflow obstruction was associated with elevated inflammatory markers and electrocardiographic ischaemia.[139] Reduced FEV_1 independently predicts cardiovascular mortality in population studies after adjusting for age, cigarette smoking, hypertension, cholesterol, and obesity.[142] A meta-analysis demonstrated an increased relative risk of 1.75 (1.54-2.01) when comparing worst and best FEV_1 quintiles.[143] However, the multivariable models were often limited, notably lacking adjustment for co-existing diabetes and cardiovascular disease.

Inflammation is itself implicated in the pathogenesis of HF. Incidence of HF was greater in Framingham subjects with elevated C-reactive protein (CRP) and cytokine levels, independent of established risk factors (hazard ratio 4.07 [95% CI

1.34-12.37], p=0.01).[144] However, two population studies found no evidence of a relationship between COPD and incidence of HF. The Cardiovascular Health Study prospectively examined 5888 elderly subjects over a mean of 5.5 years. Elevated CRP and reduced FEV_1, but not a history of COPD, were significant factors during stepwise selection of variables in this study.[145] Likewise, COPD was not an independent predictor of LVSD in the Copenhagen study.[146] Both studies relied upon self reported medical history. Such methods are particularly limited when examining conditions with diagnostic difficulties and overlapping symptoms.

1.4.5 Prognostic implications of COPD in patients with HF

Few studies focused on the prognosis of patients with HF and concomitant COPD.[97,128] However, COPD was consistently an independent predictor of death and HF hospitalisation when reported in multivariable models (Table 1.5). In many models the prognostic significance approached or exceeded that of traditional factors including male gender, diabetes, hypertension, NYHA class, and anaemia. As in all multivariable analyses, the risk relates in part to the number and type of variables adjusted for in the model. Only one study has explored the causes of increased mortality.[128] The outcomes of patients with COPD enrolled in the Valsartan Heart Failure Trial (Val-HeFT) trial were examined using multivariate models including demographic, clinical, biohumoral and treatment variables. COPD strongly predicted non-cardiovascular mortality (HR 2.50 [1.58-3.96], p<0.0001) and hospitalisations (HR 1.71 [1.43-2.06], p<0.0001), but not cardiovascular death or hospitalisations. The relationship between COPD and ischaemic or arrhythmic events has never been reported in patients with HF.

Table 1.5 Prognostic implications of COPD in patients with HF

Reference	n	COPD (%)	LVEF (%)	Outcome	Follow Up	Univariable Analysis (±95% CI)	Multivariable Analysis (±95% CI)
Gustafsson.[112]	5491	22	Any	Death	1 year	-	RR 1.36 (1.25-1.47)
Sharma.[127]	3044	9	≤ 40	Death	-	RR 1.49 (1.15-1.95) p=0.0049	RR 1.34 (1.02-1.75) p=0.0354
Lee.[85]	2624	21	Any	Death	1 year	OR 1.30 (1.07-1.58) p=0.009	OR 1.41 (1.13-1.75) p=0.003
Goldberg.[81]	2445	34	Any	Death	1 year	-	OR 1.39 (1.15-1.69)
Braunstein.[78]	122630	26	Any	Death	1 year	RR 1.31 (1.27-1.34)	RR 1.12 (1.09-1.16)
Alexander.[147]	90316	-	Any	Death	1 year	-	RR 1.19 (1.15-1.22)
Jong.[148]	38702	-	Any	Death	1 year	-	OR 1.13 (1.07-1.19) p<0.001
Krumholz.[149]	222424	-	Any	Death	30 days	-	OR 1.15 (1.12-1.18)
Martinez-Selles.[94]	1065	30	Any	Death	median 19 months	-	HR 1.6 (1.2-2.0) p=0.001
Tribouilloy.[122]	294	21	< 50	Death	5 year	-	HR 1.49 (1.04-1.95) p=0.05
Tribouilloy.[122]	368	20	≥ 50	Death	5 year	-	HR 1.61 (1.13-2.28) p=0.008
Senni.[96]	292	15	Any	Death	1 year	-	OR 1.41 (0.99-2.35) p=0.005
Agoston.[119]	448	31	Any	Death	-	-	HR 1.45 (1.10-1.92) p=0.01
Kjaergaard.[118]	388	22	Any	Death	-	-	HR 2.67 (1.98-3.59) p<0.0001
Kamalesh.[80]	495	52	< 50	Death	-	OR 1.59 (1.15-2.19) p=0.0048	OR 1.34 (0.95-1.90) p=0.095
Newton.[89]	528	9	Any	Death	mean 1257 days	HR 1.49 (1.00-2.20) p=0.049	- p=NS
Siirila Waris.[99]	620	13	Any	Death	1 year	HR 1.2 (0.80-1.87) p=0.4	- p=NS
Macchia.[97]	1020	24	Any	Death	mean 287 days	HR 1.46 (1.12-1.92) p=0.005	HR 1.42 (1.09-1.86) p=0.010
Macchia.[97]	1020	24	Any	HF hospitalisation, MI, or stroke	mean 244 days	-	HR 1.26 (1.01-1.58) p=0.04
Ansari.[77]	403	26	Any	Death or CV hospitalisation	mean 22 months	HR 1.32 (0.9-1.9) p=0.14	HR 1.39 (0.9-2.1) p=0.11
Berry.[124]	315	11	≤ 40	Death or HF hospitalisation	-	-	HF 1.61 (0.98-2.64) p=0.061
Parker.[126]	6797	7	≤ 35	Death or HF hospitalisation	-	-	OR 1.43 (1.16-1.76) p=0.0008
Braunstein.[78]	122630	26	Any	HF hospitalisation	1 year	RR 1.49 (1.45-1.53)	RR 1.40 (1.36-1.44)
Harjai.[75]	434	18	Any	HF hospitalisation	30 days	-	OR 2.2 (1.1-4.5)

CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; LVEF, left ventricular ejection fraction ('Any' denotes inclusion of all patients with heart failure); HF, heart failure; HR; hazard ratio; MI, myocardial infarction; OR, odds ratio; RR, risk ratio.

The increased risk of HF hospitalisation is unsurprising. Respiratory infections are associated with decompensation in 10-16% of admissions.[86,150-154] Concomitant COPD prolongs inpatient stay,[87,103] increases risk of readmission,[75,78,155] and independently predicts greater financial costs.[156] Respiratory disease, and in particular COPD, is a more frequently recorded comorbidity in winter.[157] The ACC/AHA guidelines advocate influenza and pneumococcal immunisation to reduce this risk.[158] Administering influenza A vaccine to elderly patients with HF during the 1991–1992 influenza epidemic reduced the rate of HF hospitalisation by 37%, and associated costs by 43%.[159]

1.5 β-blockers in COPD

1.5.1 Guidelines regarding β-blocker utilisation in HF and COPD

The ACC/AHA guidelines for the management of HF advocate 'great caution' when using β-blockers in patients with symptomatic 'reactive airways disease'.[158,160] No definition of 'reactive airways disease' is provided. Concerns stem from reports of acute bronchospasm in asthmatic patients given non-cardioselective β-blockers.[161-163] The guidelines also state that 'most patients' with COPD 'remain reasonable candidates for β-blockade'. More precise advice is lacking. By contrast, the ESC guidelines clearly state that COPD 'is not a contraindication'.[4] Low dose initiation and gradual up-titration is recommended. Furthermore, the guidance indicates that 'mild deterioration in pulmonary function and symptoms should not lead to prompt discontinuation'.

1.5.2 How many patients with HF and COPD are prescribed β-blockers?

Surprisingly few studies report the prevalence of β-blocker use in patients with HF and concomitant COPD (Table 1.6).

Table 1.6 Prevalence of β-blocker use in patients with heart failure and chronic obstructive pulmonary disease

Reference	Prevalence β-blockade (%)	Population	n	LVEF (%)	Country	Data Source
Shah.[164]	24	Community	916	Any	U.K.	UK DIN-LINK database
Iversen.[165]	27	HF hospitalisation	182	Any	Denmark	ECHOS Study Group
Macchia.[97]	16	HF hospitalisation	241	Any	Italy	Hospital discharge records
Sin.[166]	6	HF hospitalisation	3834	Any	Canada	Alberta Statistics Registry
Rusinaru.[167]	6	HF hospitalisation	156	Any	France	Hospital discharge records
Patel.[168]	80	HF hospitalisation	57	≤ 40	U.S.	Veterans Affairs Medical Centre
Krum.[169]	85	Heart failure clinic	89	LVSD	Australia	Clinic
Kotlyar.[170]	84	Heart failure clinic	31	LVSD	Australia	Clinic
Mascarenhas.[171]	86	Heart failure clinic	73	LVSD	Portugal	Clinic
Shelton.[172]	81	Heart failure clinic	124	≤ 40	U.K.	Clinic
Staszewsky.[128]	22	Clinical trial	628	< 40	Multinational	Val-HeFT

HF, heart failure; LVEF, left ventricular ejection fraction ('Any' denotes inclusion of all patients with heart failure); LVSD, left ventricular systolic dysfunction

Analysis from 152 UK general practices indicated that 24% of primary care patients with both conditions were prescribed β-blockers.[164] Italian and Danish studies observed comparable prescription levels on admission to hospital with worsening HF in 241 and 182 patients with concurrent COPD (respectively 16% and 27%).[97,165] Similarly, 22% of patients with HF and COPD enrolled in the Valsartan Heart Failure Trial received β-blockers.[128] However, four specialised HF clinics

report consistently higher use of β-blockers in patients with LVSD and COPD.[169-172] Between 81% and 86% of outpatients with COPD tolerated β-blockers. Selection bias undoubtedly contributes (i.e. patients with less severe COPD are referred to specialist clinics). In the Euro Heart Failure Survey 'pulmonary disease' was the most powerful independent predictor of β-blocker underutilisation (odds ratio 0.35 [95% CI 0.30 - 0.40]).[173] An Australian analysis revealed similar underuse of β-blockers at hospital discharge in patients with HF and airways disease (odds ratio 0.35).[174] I next examine whether such fears are justified.

1.5.3 Properties of β-blockers approved for the treatment of HF

Greater β_1-receptor affinity provides a wider division between β_1 and β_2-adrenoceptor blockade, the latter mediating bronchoconstriction. Estimates of β_1-affinity (so called 'cardioselectivity') vary according to methodology. In vitro, β_1/β_2 selectivity ratios have been derived from receptor binding studies in a wide range of tissues using different response measures, agonists and antagonists. β_1-selectivity is demonstrated in vivo through antagonism of biochemical (serum potassium, glucose and insulin) and haemodynamic (heart rate and blood pressure) responses to β_2-stimuli such as terbutaline or isoprenaline.[175] Table 1.7 outlines the properties of β-blockers approved for the treatment of HF.

Table 1.7 Properties of β-blockers approved for the treatment of HF

β-blocker	β_1-selectivity	α-antagonism	Intrinsic sympathomimetic activity	Lipid solubility	Route of elimination	Half life (hours)
Carvedilol[176]	1	+	-	moderate	hepatic	7-10
Metoprolol[177]	40	-	-	moderate	hepatic	3-7
Bisoprolol[178]	75	-	-	low	hepatic / renal	10-12
Nebivolol[179]	>300	-	-	high	hepatic	12-19

1.5.4 Randomised trials of cardioselective β-blockade in COPD

No study has prospectively examined β-blockade in patients with both HF and COPD. The evidence in those with COPD alone informs our daily decisions. Any review of 'COPD and HF' must therefore objectively appraise β-blockade in 'COPD without HF'. A Cochrane Library meta-analysis concluded that long term cardioselective β-blockade is safe and well tolerated in COPD.[2,180] This meta-analysis evaluated pulmonary function in 20 randomised, controlled, cross-over trials of cardioselective β_1-blockers in patients with COPD (Table 1.8).[181-200] No study included any patients with HF.

The evidence has many limitations. Only two studies involved more than 20 patients,[192,198] some were single rather than double-blinded,[196,197] and others lacked a placebo control.[182,192,193,196] Eleven trials involved a single treatment dose and only one lasted longer than a month.[192] The effect of long term β-blockade is therefore unknown. The 9 'long term' studies (defined as more than a single treatment dose) involved 147 young, predominantly male patients with moderate airways obstruction (mean FEV_1 1.8 litres). Extrapolation to elderly or female patients with HF therefore requires caution.

Table 1.8 Randomised controlled trials of cardioselective β-blockers in patients with COPD

Reference	n	Duration	Severe	Reversibility	Placebo Control	Double Blind	Mean FEV_1 (l)	Mean FEV_1 (% Pred)	β-blocker	Route	Dose (mg)	Reduction FEV_1 (l) (%)
Anderson.[181]	9	single dose	-	-	Yes	Yes	-	-	metoprolol propranolol	PO	100 80	-
Beil.[200]	20	single dose	-	-	Yes	Yes	-	-	atenolol propranolol	PO	100 80	-
Sorbini.[182]	8	single dose	-	-	-	Yes	1.9	-	metoprolol	PO	50, 100, 150, 200	10%
Schaanning.[183]	20	single dose	-	-	Yes	Yes	1.9	-	practolol	IV	15	6%
Perks.[189]	10	single dose	-	-	Yes	Yes	1.9	-	atenolol oxprenolol	PO	50, 100 80	-
Lammers.[184]	8	4 weeks	-	-	Yes	Yes	2.4	-	metoprolol pindolol	PO	100 bd 10 bd	0.25 0.20
Tivenius.[185]	12	2 days	-	-	Yes	Yes	1.7	50	metoprolol propranolol	PO	50 tds 40 tds	0.14 0.41
van der Woude.[199]	15	4 days	-	-	Yes	Yes	2.4	72	propranolol metoprolol celiprolol	PO	80 100 200	0.33 0.25 0.09
Ranchod.[186]	15	3 weeks	-	-	Yes	Yes	2.3	-	atenolol propranolol	PO	100 od 40 qds	0.13 0.12
Adam.[187]	10	single dose	-	Yes	Yes	Yes	1.7	-	metoprolol atenolol labetolol propranolol	PO	100 100 200 80	0.09 0.15 0.01 0.23
von Wichert.[188]	12	single dose	-	Yes	Yes	Yes	-	-	metoprolol pindolol	PO	100 5	-
Dorow.[190]	12	single dose	-	Yes	Yes	Yes	1.6	-	bisoprolol atenolol	PO	20 100	p=NS p=NS
Macquin-Mavier.[191]	9	single dose	-	Yes	Yes	Yes	-	80	bisoprolol acebutolol	PO	10 400	-
Dorow.[192]	34	12 weeks	-	Yes	Active	Yes	1.7	-	celiprolol	PO	200, 400, 600	p=NS
McGavin.[193]	9	single dose	Yes	-	-	Yes	1.1	40	metoprolol propranolol	PO	100 mg 80 mg	0.03 0.27
Sinclair.[194]	10	single dose	Yes	-	Yes	Yes	1.3	-	metoprolol propranolol	IV	0.12 mg/kg 0.06 mg/kg	0.07 0.20
Wunderlich.[198]	35	2 days	Yes	-	Yes	Yes	1.3	-	metoprolol propranolol	PO	100 bd 80 bd	16% 36%
Butland.[195]	12	4 weeks	Yes	-	Yes	Yes	-	26	metoprolol atenolol	PO	100 od 100 od	11% 10%
Fogari.[196]	10	1 week	Yes	Yes	-	-	1.3	-	atenolol celiprolol oxprenolol propranolol	PO	100 200 80 80	p=NS p=NS 14% 16%
Fenster.[197]	6	1 week	Yes	Yes	Yes	-	-	45	metoprolol	PO	50 qds	6%

The doses used were those employed for treating hypertension or angina. This contrasts with the low dose initiation and gradual titration in patients with HF. Information is particularly limited for β-blockers conferring benefit in HF: while many trials used metoprolol, only two single dose studies used bisoprolol,[190,191] and none carvedilol or nebivolol.

1.5.5 Effect of cardioselective β-blockade in COPD with reversible airflow obstruction

The long term effect of cardioselective β-blockers in patients with COPD and significant reversibility is unknown. Of the 20 trials included in the Cochrane meta-analysis, 7 involved patients with reversible airflow obstruction, defined by FEV_1 improvement of at least 15% following β_2-agonists.[187,188,190-192,196,197] FEV_1 was unaffected by either single dose or longer duration cardioselective β-blockade (-1.8% and -1.26% respectively). However, the 'long term' data derive primarily from a single randomised trial lasting just 12 weeks.[192] Celiprolol, a rarely used cardioselective β-blocker with mild β_2-agonism and α_2-antagonism, caused no significant change in FEV_1 in 34 patients with moderate reversible airflow obstruction.

Two small, single dose studies suggest the greater β_1-selectivity of bisoprolol is clinically relevant in patients with significant reversibility.[190,191] In the first, 100 mg of atenolol significantly increased airway resistance compared to 20 mg of bisoprolol.[190] In the second, acebutolol (a moderately β_1-selective blocker) but not bisoprolol inhibited the bronchodilator response to salbutamol.[191] The longest study to date examining β-blockade in COPD contradicts these results, but was not

included in the meta-analysis. In a randomised, double-blind, cross-over trial, 40 patients with mild COPD and significant reversibility received bisoprolol 5 mg or atenolol 50 mg.[201] FEV_1 declined significantly over 6 months by approximately 0.2 litres in both treatment arms. Although the study lacked a concurrent placebo group, lung function variables normalised during the placebo cross-over period, suggesting β-blockade directly caused bronchoconstriction.

The Cochrane meta-analysis reported no significant inhibition of β_2-agonist response by cardioselective β-blockers. These results derive from four small studies,[187,194,196,199] two of which excluded patients with significant reversibility.[194,199] The apparent lack of interaction between β-blockade and β_2-agonist mediated bronchodilatation is unsurprisingly given the minimal baseline reversibility. Only a single study of 10 patients, lasting one week, specifically included patients with reversible airflow obstruction.[196] Neither atenolol nor celiprolol antagonised the effect of inhaled salbutamol.

1.5.6 Effect of cardioselective β-blockade on severe airflow obstruction

The same caveats apply to the evidence for β-blockade in patients with severe COPD. The few existing studies are small, of limited duration, predominantly used metoprolol, had no dose titration and excluded patients with HF (Table 1.8). The Cochrane library separately analysed 6 trials with mean baseline FEV_1 less than 1.4 litres or 50% of normal predicted values.[193-198] No significant change occurred in FEV_1 following single dose (-0.71% [CI, -5.69 to 4.27]) or longer term β-blocker therapy (-3.11% [CI, -8.62 to 2.41]).[2] Four trials enrolled patients with fixed airflow obstruction, of which two used single doses[193,194] and another lasted just two days.[198]

In the remaining study of 12 patients, atenolol and metoprolol each significantly reduced FEV_1 by around 10% over four weeks.[195] A further two studies included patients with both severe and reversible airways obstruction, each lasting one week.[196,197] Metoprolol and atenolol caused no significant change in FEV_1 in 6 and 10 patients respectively. A recent study without placebo control also deserves mention.[202] In 50 patients with coronary artery disease and COPD (21 with severe airflow obstruction), pulmonary function was unaffected by metoprolol over 3 months.

1.5.7 Effect of cardioselective β-blockade on symptoms

Only one patient in each of the β-blocker and placebo groups experienced increased respiratory symptoms in the Cochrane meta-analysis.[2] The longer duration treatment ranged from just 2 days to 12 weeks. Over short periods patients may curtail typical daily activities, thus underestimating the effect on symptoms. Furthermore, many studies only describe dyspnoea of sufficient magnitude to merit voluntary self-reporting. Moderate and less acute symptoms may be inadequately assessed. The perception of respiratory effort and associated distress is subjective and variable with time, reflecting a complex interaction between psychology and physiology.[203] No trial formally graded dyspnoea at baseline and follow-up using validated scales. Quantification based on physical exertion also fails to reflect mental health and social functioning.[204] The effect of β-blockade on health related quality of life has never been assessed in patients with COPD.

Almost all trials evaluating β-blockade in HF excluded patients with significant pulmonary disease, documented COPD, or bronchodilator therapy (Table 1.9).

Table 1.9 Exclusion criteria, prevalence of COPD and respiratory symptoms in major β-blocker trials

Acronym	Year	Exclusion Criteria	Prevalence Of COPD	β-Blocker	Respiratory Symptoms (β-blocker vs placebo)
MDC [205]	1993	obstructive lung disease requiring β_2-agonists	not reported	metoprolol	not reported
CIBIS I [206]	1994	asthma	not reported	bisoprolol	not reported
US Carvedilol Trials[207]	1996	any condition limiting exercise or survival, such as pulmonary disease[208]	not reported	carvedilol	cough 8% vs 10%
MOCHA [209]	1996	obstructive pulmonary disease requiring oral bronchodilator or steroid therapy	not reported	carvedilol	respiratory disorder 5% vs 11%
PRECISE [210]	1996	any condition limiting exercise or survival, such as pulmonary disease	not reported	carvedilol	not reported
ANZ [211]	1997	chronic obstructive airways disease, or current treatment with a β-agonist	not reported	carvedilol	not reported
CIBIS II [212]	1999	reversible obstructive lung disease[213]	not reported	bisoprolol	not reported
MERIT-HF [214]	1999	contraindication to β-blockade[215]	not reported	metoprolol	not reported
RESOLVD [216]	2000	chronic reversible airways disease requiring therapy	not reported	metoprolol	not reported
BEST [217]	2001	contraindication to β-blockade,[218] or β-agonists	not reported	bucindolol	not reported
COPERNICUS [219]	2001	severe primary pulmonary disease, or contraindication to β-blocker therapy	not reported	carvedilol	not reported
CAPRICORN [220]	2001	significant pulmonary impairment,[221] or therapy with inhaled β_2-agonists or steroids	not reported	carvedilol	not reported
COMET [222]	2003	history of asthma or chronic obstructive pulmonary disease	not reported	carvedilol, metoprolol	not reported
CIBIS III [223]	2004	obstructive lung disease contraindicating bisoprolol treatment[224]	not reported	bisoprolol	not reported
SENIORS [225]	2005	regular inhaled bronchodilators,[226] or history of bronchospasm or asthma	not reported	nebivolol	not reported

Those involving bisoprolol had less stringent criteria, though investigators may avoid recruiting patients with severe airflow obstruction. Only the Multicenter

Oral Carvedilol Heart failure Assessment trial reported respiratory adverse events.[209] This trial excluded patients with COPD requiring oral bronchodilator or steroid therapy, so extrapolation to patients with severe or reversible airflow obstruction is inadvisable. Patients receiving carvedilol experienced fewer 'respiratory disorders' (5% vs 11%, p=0.09), with 'approximately equivalent' frequency of 'upper respiratory illness' and 'cough'. Tolerability in the U.S. Carvedilol Studies was also biased by the open label β-blocker run-in period prior to randomisation. No trial specifically reported bronchospasm. Whether this reflects genuine tolerability, limited detection strategies, or exclusion of patients with airflow obstruction is unclear.

1.5.8 Effect of non-cardioselective β- and α-blockade on airflow obstruction

Carvedilol is the only non-cardioselective β-blocker approved for treating HF. Most of the trials in the Cochrane meta-analysis reported adverse side effects with other non-selective β-blockers. Propranolol significantly reduced FEV_1,[185-187,193,194,196,198,199] antagonised β-agonists,[185,187,194,196,198,199] increased dyspnea,[185,186,193,194,198] and even necessitated withdrawal of patients from studies.[185,186,193,198] The purported mitigating effect of α-blockade is circumstantial at best. In a small study involving 10 patients, FEV_1 and response to salbutamol were unchanged following single doses of labetolol.[187] However, at equipotent antihypertensive doses labetolol exerts half the β-blocking effect of the other β-blockers investigated, thus producing less bronchoconstriction.[187]

Two retrospective Australian analyses have assessed tolerability of carvedilol in patients with HF and airflow obstruction. The first studied 808 consecutive

patients commencing open label treatment.[169] Among 89 patients with coexistent COPD or asthma, 85% tolerated carvedilol. No comment was made regarding the severity and reversibility of airflow obstruction, or the reasons for intolerance. The analysis also excluded patients in whom carvedilol was never initiated due to anticipated β-blocker intolerance. The results undoubtedly reflect selection bias rather than true tolerability. The second study examined 31 patients with concomitant moderate COPD without significant reversibility (mean FEV_1 62% predicted, reversibility 4%).[170] 84% tolerated carvedilol, with only one patient withdrawing due to wheeze. However, patients were predominantly young men and only 39% used inhaled bronchodilators. Applicability to 'real world' patients is limited.

A recent retrospective UK report concluded that most patients with HF and COPD safely tolerate β-blockers.[172] Over half of those prescribed a β-blocker received carvedilol. Among 356 patients attending a HF clinic, 124 (35%) were diagnosed with 'obstructive airways disease' using handheld spirometry at baseline. Many diagnostic pitfalls exist.[1] The reduced FEV_1 and FEV_1:FVC ratio may reflect restrictive ventilation, fluid overload, and the elderly population (mean age 71 years). Notably, 24% of patients said to have moderate to severe airways obstruction had never smoked. The lack of bronchodilator therapy was likewise surprising given the beneficial effects on symptoms, pulmonary function, quality of life, and frequency of exacerbations.[5] Only 43 patients (12%) were receiving bronchodilators despite three times this number having significant airways disease. To conclude, there are no robust data supporting the safety or efficacy of carvedilol in patients with moderate to severe or reversible airways disease.

1.5.9 Effect of β-blockade on mortality in patients with HF and COPD

In observational studies, use of β-blockers is associated with better survival in patients with HF and concurrent COPD,[128,166,227] a finding corroborated in post MI populations (Table 1.10).[228,229] None of the studies assessed pulmonary function, limiting inference to patients with severe or reversible airflow obstruction. Prescribing bias is inevitable due to perceived or documented intolerance to β-blockers. This is compounded by recruitment bias in analyses from clinical trials, whose enrolment criteria often excluded patients with significant pulmonary disease. The lower mortality of patients receiving β-blockers may also reflect less severe lung disease.

Table 1.10 Association between β-blockade and mortality in patients with cardiovascular disease and COPD

Reference	Population with concurrent COPD	n with COPD	Prevalence of β-blockade (%)	Follow-up	Mortality
Staszewsky.[128]	HF	628	22	mean 23 months	17% vs 31%, p<0.001
Sin.[166]	HF	3834	6	median 21 months	HR 0.78 (0.63-0.95)
Gottlieb.[228]	post MI	41814	22	2 year	HR 0.60 (0.57-0.63)
Chen.[229]	post MI	6628	31	1 year	HR 0.85 (0.73-1.00)

COPD, chronic obstructive pulmonary disease; HF, heart failure; HR, hazard ratio; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction

In the Valsartan Heart Failure Trial, 140 (22%) of the 628 participants with physician recorded COPD received β-blockers.[128] Mortality over a mean of 23 months was approximately 17%, as opposed to 31% in those with HF and COPD not prescribed β-blockers (p<0.001). No statistical adjustment for baseline differences was performed. A retrospective Canadian study of 11942 elderly patients

hospitalised for HF undoubtedly more accurately represents real life.[166] Although the proportion with LVSD was unknown, just 242 (6%) of the 3834 patients with concurrent COPD received β-blockers. Mortality during median follow-up of 21 months was lower in those prescribed β-blockers, after comprehensive adjustment for age, sex, comorbidity and propensity scores (HR 0.78 [95% CI 0.63-0.95]).

1.5.10 Effect of β-blockade on morbidity in patients with HF and COPD

The long term impact of β-blockade on COPD exacerbations is unknown as regards to frequency, severity, pulmonary function, primary care burden and hospitalisations. This is particularly important in patients with HF. Should bronchospasm necessitate abrupt β-blocker withdrawal, rebound ischaemia, ventricular arrhythmias and death may ensue.[230]

1.6 β-agonist in HF

1.6.1 Physiological rationale for adverse β-agonist effects

Reduced organ perfusion in heart failure results in a compensatory increase in adrenergic drive. Adrenaline and noradrenaline stimulate ventricular contraction and increase vascular resistance, maintaining cardiac output and blood pressure. Longer term, increased mechanical stress, myocardial oxygen demand and ischaemia combine with maladaptive adrenergic signalling to depress myocardial function. β_1 and β_2 adrenoceptors mediate noradrenaline toxicity, fibrosis and necrosis. Down regulation of β_1 receptors with preservation of the β_2 subpopulation reduces the β_1/β_2

ratio.[231] The chronotropic and inotropic responsiveness (and likewise vulnerability) of the failing myocardium to β_2-agonists thereby assumes greater importance.[232,233]

β_2-agonists exert numerous unfavourable cardiovascular effects: tachycardia, hypokalaemia, QTc prolongation, peripheral vasodilatation, disturbed autonomic modulation and depressed heart rate variability.[234-237] In susceptible patients, β_2-agonists may precipitate ischemic events.[238,239] Hypoxia, hypercapnia, acidosis and excess sympathetic activity in pulmonary disease all potentially amplify these sequelae.[234,240,241] When combined with the arrhythmic substrate of left ventricular dysfunction,[242] the risk of life threatening arrhythmias cannot be discounted. However, theoretical concerns may be misplaced. Although β-agonists may exacerbate hypokalaemia associated with diuretics, hyperkalaemia induced by intensive renin angiotensin inhibition may conversely be reduced. The pros and cons of β-agonist use in patients with HF and COPD are rarely considered. Even the prevalence of β-agonist prescription has only been reported twice (37% and 74%).[97,128] Research is needed to define the overall impact of β-agonists in contemporary populations.

1.6.2 Cautions regarding the adverse associations between β-agonists and HF

β-agonists are associated with incident HF in patients with pulmonary disease, and with increased mortality and HF hospitalisation in those with existing HF or LVSD (Table 1.11). However, the reported adverse associations merit careful scrutiny. The evidence derives from retrospective cohort or case control analyses, all of which equated drug dispensing with drug use. Three fundamental issues undermine conclusions: limited multivariate adjustment; confounding by collinear

pulmonary disease; and bias by indication. No causality may be inferred. Multivariable analyses are often restricted in epidemiological studies due to residual confounding by unmeasured covariates. Cardiovascular risk factors and diseases both cluster in patients with COPD, along with underuse of β-blockers.[227,243]

Table 1.11 Association between β-agonists and heart failure

Reference	Population	Route	Bronchodilator	Study Design	n	Outcome	Risk associated with bronchodilator use [95% CI]
Martin 1998.[244]	asthma	oral	bambuterol	cohort	8098	HF	RR 3.41 [1.99-5.86], p<0.0001
		inhaled	salmeterol	cohort	15407	HF	RR 1.10 [0.63-1.91], p=0.7
Coughlin 1995.[245]	general population	oral	β-agonist	case control	387	DCM	OR 3.4 [1.1-11.0]
		inhaled nebulised	β-agonist	case control	387	DCM	OR 3.2 [1.4-7.1]
Sengstock 2002.[246]	cardiology clinic	inhaled	β-agonist	case control	190	DCM	OR 1.0
Macie 2008.[247]	COPD or asthma	inhaled	β-agonist	case control	59336	HF hospitalisation	OR 1.74 [1.60-1.91]
Au 2004.[248]	HF	inhaled	β-agonist	case control	1121	HF hospitalisation	OR 1.5 [0.8-2.8] 1-2 canisters OR 2.1 [1.0-4.3] ≥ 3 canisters
	general medical clinics	inhaled	β-agonist	case control	13012	HF hospitalisation	OR 1.3 [0.9-1.8] 1-2 canisters OR 1.1 [0.8-1.6] ≥ 3 canisters
Au 2003.[249]	LVSD	inhaled	β-agonist	cohort	1529	death	RR 0.9 [0.5-1.6] 1 canister / month RR 1.4 [0.9-2.2] 2 canister / month RR 2.0 [1.3-3.2] 3 canister / month
Singer 2008.[250]	acute HF without COPD	inhaled	any bronchodilator	cohort	7299	death IV vasodilator use ventilation	OR 1.02 (0.67-1.56) OR 1.40 (1.18-1.67) OR 1.69 (1.21-2.37)

ACQUIP, Ambulatory Care Quality Improvement Project; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DCM, idiopathic dilated cardiomyopathy; HF, heart failure; IV, intravenous; LVSD, left ventricular systolic dysfunction; OR, odds ratio; RR, relative risk

Pulmonary disease may itself cause cardiac injury through hypoxia, arrhythmias or even atherosclerotic mechanisms.[139] The poor outcomes attributed to β-agonists may reflect the disease for which they are prescribed. Separating the two

is difficult. Dose response relationships are limited without adjustment for severity of airflow obstruction and cumulative smoking burden.[239,249] Patients utilising more bronchodilators may simply have more severe pulmonary disease. The indication for bronchodilator prescription or utilisation may confound results. Physicians may mistakenly prescribe β-agonists or patients may increase β-agonist use for symptoms of HF. Concurrent therapy with theophylline or anticholinergics confuses matters further as both are associated with adverse cardiovascular outcomes.[251,252] Finally, β-agonists perhaps unmask rather than cause left ventricular dysfunction, as suggested by the higher risk observed early after prescription.[244]

1.6.3 β-agonists and incident heart failure.

Five reports have addressed the association between β-agonists and incident HF in the general population or those with pulmonary disease.[244-248] Prescription event monitoring collates physician reports of adverse events associated with newly launched drugs. Oral bambuterol, but not inhaled salmeterol, was associated with an increased incidence of HF in 8098 patients when compared with the reference drug nedocromil (RR 3.41 [95% CI 1.99-5.86], $p<0.001$).[244] However, the bambuterol cohort received fewer prescriptions for asthma (57.3% vs 70.2%) and more 'other' indications (12.8% vs 2.8%). Bambuterol may therefore have unmasked previously undiagnosed HF, as suggested by the greater risk in the first month of exposure compared with months 2 to 6 (respectively 4.41 [1.90-10.27] vs 2.67 [1.30-5.47]).

Two case control studies assessed the risk of idiopathic dilated cardiomyopathy defined by echocardiography associated with β-agonists.[245,246] Both suffer the inherent failings of case control methodology,[253] namely that selection bias

arises if controls are not representative of the population at risk, or independent of the exposure of interest. The numbers of events were limited, resulting in wide confidence intervals and statistical uncertainty. Oral β-agonists were associated with a 3-fold increased risk in 387 patients recruited from the Washington DC area (OR 3.4 [1.1-11.0]).[245] By contrast, the Detroit ABCHF study of 197 patients observed no significant relationship with inhaled β-agonists.[246] Although differences between oral and inhaled administration are possible, the disparity most likely relates to choice of control groups. Whereas the Washington study selected community-based controls using random digit dialling, ABCHF employed clinic-based controls with ischemic cardiomyopathy. The former is confounded by biases such as socioeconomic status when using telephone controls, the latter by the association between β-agonists and ischemic events.

Two nested case control studies yielded equally conflicting results.[247,248] 782 subjects and 12230 controls were selected from the multicentre Ambulatory Care Quality Improvement Project (ACQUIP), which examined health care reporting from general medical clinics.[248] Use of 1 to 2 β-agonist canisters per month was associated with HF hospitalisation (OR 2.6 [2.0-3.5]). However, the relationship failed to achieve significance after adjusting for age, cardiovascular comorbidity, β-blocker prescription and presence of COPD (OR 1.3 [0.9-1.8]). By contrast, the adjusted 1 year risk of HF hospitalisation among patients with COPD or asthma selected from the Manitoba Health database was increased in those receiving β-agonists (OR 1.74 [1.60-1.91]).[247] Whether inhaled β-agonists are implicated in the development of HF therefore remains uncertain.

1.6.4 Oral β-agonists in heart failure

Numerous small, short term controlled studies have examined the oral β-agonists pirbuterol, prenalterol, salbutamol and terbutaline in patients with HF.[254] The majority demonstrated acute haemodynamic improvements, including ejection fraction, cardiac index and pulmonary capillary wedge pressure.[255,256] However, only 3 studies recruited at least 20 patients and lasted longer than a month.[255-257] Although symptoms and exercise tolerance improved, no β-agonist produced a sustained improvement in systolic function. The trials lacked statistical power and were of insufficient duration to identify longer term impairment of systolic performance. Significant arrhythmias were however observed. Six of 20 patients with advanced HF developed recurrent ventricular tachycardia with oral salbutamol which subsided once discontinued, although two required cardioversion.[255]

Two large, randomised controlled trials investigated oral xamoterol, a partial β_1-agonist. The first randomised 433 patients with mild to moderate HF to receive xamoterol, digoxin or placebo.[258] Xamoterol improved exercise capacity, dyspnoea and fatigue. The Xamoterol in Severe Heart Failure Study aimed to extend these findings in 516 patients with NYHA class III and IV symptoms. However, the trial was terminated prematurely due to excess mortality in the xamoterol group within 100 days of randomisation (9.1% vs 3.6%, p=0.02).[259] Both sudden death and progressive pump failure contributed to the increased mortality.

Respiratory guidelines favour inhaled over oral bronchodilators due to rapid therapeutic action, greater efficacy, and fewer side effects.[5] However, neither cardiologic nor pulmonary societies specifically counsel against oral agents in patients with cardiovascular disease.[4,5,44,160] This lack of guidance is concerning: in

the Val-HeFT trial, 73% of patients with HF and concurrent COPD were prescribed oral β_2-agonists.[128]

1.6.5 Nebulised β-agonists in heart failure

Nebulised doses are typically ten times greater than standard inhalers. Two facts should be considered. Systemic adverse effects are dose dependent,[260,261] and pulmonary absorption delivers β-agonists to the heart without first pass metabolism. Nebulised β-agonists may precipitate arrhythmias and myocardial ischaemia.[262,263] Four acute studies recruiting 44 patients in total have administered nebulised β_2-agonists to patients with HF.[264-267] No adverse events were reported. In 13 patients, cardiac output and ejection fraction significantly increased within 10 minutes of inhalation, returning to baseline after 30 minutes.[264] The remaining three studies observed a reduction in airflow obstruction following nebulised salbutamol, but no consistent improvement in exercise capacity.[265-267] Given the limited patient numbers, clinical judgment is paramount. Increasing from 2.5mg to 5mg salbutamol produces only limited incremental bronchodilatation.[268,269] Clinicians should minimise both the dose and frequency of nebulised therapy when treating patients with HF and concurrent COPD.

1.6.6 Inhaled β-agonists in heart failure

Standard metered dose β-agonist inhalers produce only minor systemic and biochemical abnormalities.[260,261,270] Whether these contribute to adverse events in patients with HF or LVSD is debatable.[248,249] Among 1529 patients with LVSD identified retrospectively through imaging records, 363 were dispensed β-agonist

canisters in the 90 days prior to the index echocardiogram.[249] All cause mortality and HF hospitalisation within 1 year were associated with β-agonist use, risk increasing with the average number of canisters dispensed per month. After covariate adjustment, risk of HF admission was: 1.3 [0.9-2.0] (1 canister / month); 1.7 [1.2-2.5] (2 canisters / month); 2.0 [1.3-3.0] (≥ 3 canisters / month). Risk of death was similarly increased: 0.9 [0.5-1.6] (1 canister / month); 1.4 [0.9-2.2] (2 canisters / month); 2.0 [1.3-3.2] (≥ 3 canisters / month). However, any association is undermined by the indication for β-agonist use: increasing dyspnoea and resulting β-agonist prescription may simply reflect worsening HF. Without markers of HF severity the multivariate model was unable to adjust for such confounding.

In the ACQUIP case control study,[248] β-agonists were associated with HF hospitalisation among those with existing HF (OR 1.8 [1.1-3.0]). Adjustment for age, cardiovascular comorbidity, β-blocker prescription, presence of COPD and a marker of disease severity (steroid use) reduced the magnitude of association (OR 1.6 [1.0-2.7]). Adding smoking status and pack year history to the multivariate model rendered the relationship non-significant (OR 1.5 [0.8-2.8]). The findings reinforce concerns that the purported adverse effects of β-agonists relate to underlying pulmonary disease and clustering of cardiovascular risk factors.

A single study has prospectively investigated inhaled β-agonists, administering salmeterol 84 μg twice daily to 8 patients with NYHA class II or III heart failure.[271] FEV_1 improved by 6% compared with placebo (p=0.01). Concomitant airflow obstruction limits interpretation: mild COPD was not excluded, baseline FEV_1 was reduced in all patients, and smoking history not documented. The pharmacokinetic data proved more revealing. The steady state trough and peak

concentrations and half-life of salmeterol were at least double those reported in patients with asthma. Physicians must be wary of diminished β-agonist hepatic metabolism in patients with HF.

1.6.7 β-agonists in acute heart failure

Inhaled β-agonists have never been prospectively evaluated in patients with decompensated HF, although the physiological actions are appealing: enhanced cardiac output, reduced peripheral vascular resistance and bronchodilatation.[272] However, numerous clinical trials have tested therapies with favourable haemodynamic activity in patients with acute heart failure, none of which improved mortality.[4] Analogies with intravenous inotropic drugs acting through adrenergic pathways are inescapable. Acute improvement may belie myocardial injury leading to increased mortality.[4,273] Evidence from 7299 patients without COPD enrolled in the Acute Decompensated Heart Failure National Registry supports these concerns.[250] Bronchodilators were administered to 14.3% of patients and associated with greater requirement for intravenous vasodilators (adjusted OR 1.40 [1.18-1.67]) and mechanical ventilation (OR 1.69 [1.21-2.37]). Hospital mortality was similar regardless of bronchodilator therapy. Physicians should use bronchodilators cautiously in those without established pulmonary disease.

1.6.8 Interaction between β-blockers and β-agonists

The evidence supporting an interaction between β-blockers and β-agonists is circumstantial and derives largely from patients suffering myocardial infarction. Less benefit was apparent in clinical trials using β-blockers with intrinsic

sympathomimetic activity post infarct.[274] β-blocker use was not associated with lower mortality among patients receiving concurrent β-agonists in the Cooperative Cardiovascular Project.[229] Conversely, the risk of acute coronary syndromes associated with β-agonists was lessened by concurrent β-blockade in a case control study using data from the Veterans Administration ACQUIP trial (p for interaction < 0.0005).[239] The aforementioned interaction between β-blockers and β-agonist bronchodilator response must also be considered. While cardioselective β-blockers permit bronchodilatation, non-cardioselective β-blockers inhibit β-agonist response. This raises an interesting clinical conundrum – though symptomatically less well tolerated, would non-selective β-blockade reduce the possible adverse cardiovascular effects of β_2-agonists more than cardioselective β_1-blockade?

1.7 Aims of the thesis

Critical appraisal of the existing literature has revealed an array of diagnostic, epidemiological and therapeutic questions. The crude prevalence of COPD in patients with HF has been extensively reported. Temporal trends, age and gender variations, and socioeconomic differences all require clarification. Although these chronic diseases are predominantly managed in the community, the evidence largely derives from cohorts hospitalised with worsening HF. The epidemiology and management of patients with HF and concurrent COPD in primary care is therefore particularly important. The prognostic implications of COPD in patient with HF likewise merit careful examination. The causes of increased mortality are unclear, as is the relationship between COPD and ischaemic or arrhythmic events.

The opposing therapies of β-blockers and β-agonists undoubtedly pose the greatest clinical conundrum. Prescribing rates for β-blockers have progressively increased in patients with HF.[275] Whether utilisation has improved in those with concurrent COPD is unknown. Reluctance to prescribe β-blockers stems from the weakness of existing evidence. First and foremost, β-blockade has never been studied in patients with HF and COPD. Even among patients with COPD alone, the long term impact of β-blockade on pulmonary function, symptoms and quality of life is uncertain. Clinical practice necessitates balancing risk and benefit. Both are poorly defined. The morbidity and mortality benefits of β-blockade in patients with HF are incontrovertible. The evidence in those with concurrent COPD is rudimentary by comparison. β-agonists present similar problems. Given the potential for adverse effects, the characteristics and outcomes of patients prescribed bronchodilators are remarkably ill defined. The studies presented in this thesis aim to address these deficits, and in doing so extend our understanding of this often overlooked group of patients.

Chapter 2

Methods

2.1 Study design

The following methods provide the study protocol for my initial investigation of bisoprolol in patients with HF and concurrent COPD.

2.1.1 Hypothesis

The principal research objective is to demonstrate cardioselective β-blockade using bisoprolol is not inferior to placebo with regard to pulmonary function in patients with HF and coexistent moderate or severe COPD with or without significant reversibility.

2.1.2 Specific research objectives

A comprehensive literature search was performed utilising MEDLINE, CINAHL, EMBASE and Cochrane Database of Systematic Reviews. Following review of all identified literature this research will specifically address the following areas in which current evidence of β-blockers use in COPD is limited.

1) coexistent heart failure.
2) moderate to severe airflow obstruction.
3) presence of reversible airflow obstruction.
4) quantification of dyspnoea.
5) health related quality of life.
6) response to inhaled β_2-agonist.
7) limited follow up duration.

2.1.3 Design

The study is a randomised, double-blind, placebo-controlled, single domain, clinical trial examining the effect on pulmonary function of cardioselective β-blockade using bisoprolol compared with placebo in patients with HF and coexistent moderate or severe COPD with or without significant reversibility.

2.1.4 Sample size calculation

For the primary outcome FEV_1, a sample size of 63 in each group, using a confidence interval approach to equivalence and a two group 0.05 one-sided t-test, will have 80% power to reject the null hypothesis of non-equivalence (difference in means 0.20 litres or further from zero in the same direction) in favour of the alternative hypothesis of equivalence (no significant difference in means of β-blocker and placebo groups), assuming the expected difference in means is 0.00 and the common standard deviation is 0.45 litres. The mean FEV_1 standard deviation of 0.45l was assumed from previous studies involving patients with COPD.[184,193,276,277]

$n = \frac{2s^2}{\Delta^2}\left[z_{(1-\alpha)} + z_{(1-\beta)}\right]^2$ for a 100(1-α)% one sided confidence interval.

$$n = \frac{2(0.45)^2}{0.2^2}\left[z_{(1-0.05)} + z_{(1-0.2)}\right]^2 = 10.125\times(1.64 + 0.84)^2 = 62.3$$

For the secondary outcomes SF-36 Physical and Mental Component Summary scores, a sample size of 49 patients in each group is required to detect a difference in means of 6, assuming a standard deviation of 10.5, power of 80% and significance level of 5%.

2.1.5 Inclusion criteria

Subjects with stable chronic heart failure and coexistent moderate to severe chronic obstructive pulmonary disease and presence or absence of reversible airflow obstruction.

a) **Stable heart failure**

- symptomatic NYHA II or III chronic heart failure.
- left ventricular systolic dysfunction – left ventricular ejection fraction < 40% measured by echocardiography or radionuclide ventriculography.
- stable cardiovascular state > 2 weeks before the study protocol.
- unchanged doses of concomitant cardiovascular therapy including angiotensin converting enzyme inhibitors (ACEI), aldosterone antagonists, digitalis, vasodilators, aspirin, statin, calcium channel blockers.

b) **Chronic obstructive pulmonary disease**

- either moderate ($50\% \leq FEV_1 < 80\%$) or severe ($30\% \leq FEV_1 < 50\%$) GOLD classification of severity.
- $FEV_1/FVC < 70\%$.
- minimum 10 pack year smoking history.
- with or without significant reversibility defined by $FEV_1 \geq 12\%$ (and 200 ml) increase 30 minutes after short acting inhaled β_2-agonist salbutamol.

- stable respiratory state for 2 weeks before the study protocol, including no respiratory tract infections, unchanged doses of concomitant respiratory therapy, and no objective evidence of increasing bronchoconstriction.

2.1.6 Exclusion criteria

a) β-blocker contraindications

- resting bradycardia less than 60 beats per minute.
- sick sinus syndrome.
- trifascicular block.
- second or third degree atrioventricular block unless treated with a pacemaker.
- supine or sitting hypotension systolic arterial pressure < 100 mmHg during initiation.
- cardiogenic shock, intractable pulmonary oedema.
- acute heart failure requiring intravenous inotropic or mechanical support.
- standard clinical criteria of asthma including family history of asthma, young age of symptom onset, response to provocative stimuli.
- peripheral arterial disease with symptoms at rest, Raynaud's syndrome.
- unstable insulin dependent diabetes mellitus.
- untreated phaeochromocytoma.
- metabolic acidosis.
- previously documented hypersensitivity to bisoprolol or any excipients.

b) Confounding pulmonary disease

- pulmonary fibrosis.

c) Medication

- non-dihydropyridine (diltiazem / verapamil) calcium channel blockers.
- clonidine.
- monoamineoxidase inhibitors.
- class-I antiarrhythmic drugs e.g. disopyramide, quinidine.
- parasympathomimetic drugs.
- alternative β-blockers.
- prostaglandin synthetase inhibiting drugs, excluding aspirin.
- ergotamine derivatives.
- barbiturates.
- rifampicin.
- mefloquine.
- any investigative trial drug previous one month.

d) Comorbidity

- recent (2 weeks) coronary percutaneous intervention or coronary artery bypass graft surgery.
- haemodynamically significant valvular disease or hypertrophic cardiomyopathy.
- active myocarditis or pericarditis.
- recent (2 weeks) cerebrovascular accident or transient ischaemic attack.
- serious concurrent systemic disease, such as malignancy, resulting in likely reduced life expectancy.

- significant renal (serum creatinine > 300 μmol/L), hepatic (ALT / AST > 3 times the upper limit of normal), haematological (haemoglobin < 10 g/dL), metabolic, gastrointestinal or endocrine dysfunction.
- pregnancy, childbearing potential with inadequate contraception, breast feeding.

e) General

- mental or legal incapacitation.
- patients unable or unwilling to provide informed consent.
- anticipated poor compliance with the intervention.
- drug or alcohol abuse within the last 6 months.
- extensive travel planned during the trial period.
- planned discharge to long term residential care.
- residence outside the hospital's catchment area.

2.1.7 Study flow chart

Patients attend for one baseline and initiation visit (Day 0 Study Protocol) and 5 follow up visits over 4 months (Weeks 2, 4, 8, 12, 16 Study Protocol). Participants were invited to attend the research unit at 8.30 on each study day after a light breakfast to minimise changes in bioavailability due to food intake. Patients were advised to temporarily cease bronchodilator therapy and abstain from smoking tobacco for 12 hours prior to attendance. Study medication was omitted on the morning of visit days. Subjects were observed for 4 hours on test days and allowed home following pulmonary function testing.

Table 2.1 Study flow chart

Visit Number	1	1	2	3	4	5	6
Week	0	0	2	4	8	12	16
Bisoprolol Dose	0	1.25	2.5	5	7.5	10	10
Baseline characteristics	×	-	-	-	-	-	-
Consent	×	-	-	-	-	-	-
B-type natriuretic peptide	×	-	-	-	-	-	-
Electrocardiogram	×	-	-	-	-	-	×
Physical examination	×	×	×	×	×	×	×
Concomitant medication	×	-	×	×	×	×	×
Medication Compliance	-	-	×	×	×	×	×
Medication Dispense	-	×	×	×	×	×	×
Short Form 36 (SF-36v2)	×	-	×	×	×	×	×
Respiratory Questionnaire	×	-	×	×	×	×	×
Minnesota (MLHFQ)	×	-	×	×	×	×	×
PEFR 0, 1, 2, 3, 4 hours	-	×	×	×	×	×	×
Spirometry	×	×	×	×	×	×	×
FEV_1 Reversibility	×	×	×	×	×	×	×
TLC, RV, FRC	×	×	×	×	×	×	×
T_LCO, KCO	×	-	-	-	-	-	×

Each visit included evaluation of symptoms, physical signs, pulse oximetry, health status, peak expiratory flow, spirometry and body plethysmography. All patients were clinically euvolaemic at the time of pulmonary function testing. Carbon monoxide transfer factor, electrocardiography and arterialised earlobe capillary blood gases were performed at study onset and completion. Health status was assessed using one generic and two disease specific instruments at each visit: the Short Form 36 (SF-36), Chronic Respiratory Questionnaire (CRQ) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ).[278]

2.1.8 Trial completion.

After completion of the 4 month follow up period patients were weaned off medication and the physician originally responsible for the patient's care contacted to

arrange appropriate follow up. Blinded down titration using bisoprolol or equivalent placebo commenced after the final visit. The dose was halved (rounding up) for one week. e.g. 5 mg from 10 or 7.5 mg, 2.5 mg from 5 mg, 1.25 mg from 2.5 mg. The dose was halved for a second week following the first down titration. e.g. 2.5 mg from 5 mg, 1.25 mg from 2.5 mg. All study medication was discontinued after these 2 weeks. Trial completion was defined as the date of the last treatment visit for the last patient. All randomised treatment allocations were unblinded following trial completion.

2.2 Study visits

2.2.1 Baseline characteristics

An electronic case report form (CRF) was constructed using Microsoft Access 2003 for Windows database software (Microsoft Corporation, Seattle, Washington). Age, gender, height, weight, smoking status, year started and stopped smoking, and cigarettes per day were recorded. The following cardiac and non-cardiac comorbidities were recorded in checkbox fashion: hypertension, hypercholesterolaemia, type I diabetes mellitus, type II diabetes mellitus, elevated body mass index, clinical angina, previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, atrial fibrillation, peripheral arterial disease, transient ischaemic attack, cerebrovascular accident, permanent pacemaker, cardiac resynchronisation therapy, mitral regurgitation, aortic stenosis, aortic regurgitation, tricuspid regurgitation, chronic renal failure, osteoarthritis, rheumatoid arthritis, osteoporosis, inflammatory bowel disease.

2.2.2 Physical examination

Height in metres and weight in kilograms were measured at the initial visit, allowing calculation of body mass index. Cardiorespiratory examination recorded the presence of elevated jugular venous pressure, peripheral pitting oedema, pulmonary crepitations and auscultatory signs of bronchospasm (wheeze). Pulse oximetry was measured before, 2 and 4 hours post β-blocker. Earlobe capillary sampling was performed on the first and last days.

Heart rate was measured before, 2 and 4 hours post β-blocker after subjects were seated for 5 minutes from the left radial pulse, immediately prior to measuring blood pressure. Blood pressure was measured using a standard mercury sphygmomanometer in both arms at the initial assessment unless a concomitant condition favoured the use of a particular arm. The arm with the higher average systolic blood pressure reading was used for blood pressure determination throughout the study. Korotkoff Phase V was used as the criterion for diastolic blood pressure. All measurements were read to the nearest 2 mm Hg.

2.2.3 Electrocardiography

A 12 lead electrocardiogram (ECG) was recorded and computer analysed with the subject rested for 5 minutes in the supine position. One experienced observer interpreted results. The following information was recorded: ventricular rate, PR interval, QRS duration, QT_c interval, rhythm, AV block (1° / 2° / 3°), evidence of previous myocardial infarction, left ventricular hypertrophy, ST-T wave changes.

2.2.4 B-type natriuretic peptide

Worsening of symptoms, particularly of dyspnoea or wheeze, was differentiated in standard fashion. This included assessment of pulse, blood pressure, oxygen saturation, temperature, peak expiratory flow, clinical examination, blood tests including white cell count and C-reactive protein, chest radiograph and sputum culture. In the event of diagnostic uncertainty, B-type natriuretic peptide would be compared against a baseline sample.

Venous blood sampling was performed at baseline in a standardised fashion from the antecubital fossa with the patient in the supine position for a minimum of 30 minutes prior to venesection. Standard risks associated with the use of sharp instruments were minimised with adherence to appropriate procedures for handling sharps. 10 mls of venous blood was collected in 2 pre-prepared chilled 5 mL tubes containing EDTA. These were centrifuged at 3000 rpm for 15 mins with refrigeration at 5°C. The supernatant was removed and placed in separate freezer containers labelled with the patient subject number and stored frozen at -20˚C until required. B-type natriuretic peptide concentration would be measured using a validated and commercially available immunoassay (Roche diagnostics, Mannheim, Germany). Identifiers were removed and the samples destroyed following completion of the experimental protocols.

2.2.5 Symptom evaluation

Symptom evaluation was performed according to standard reference manuals for the rating tools, with results recorded directly into the electronic case report form. Three tools were employed.

a) Short Form 36v2

The SF-36v2 is the most widely evaluated generic health outcome measure, with experience documented in 4000 publications describing 200 diseases and conditions. It comprises 36 questions derived from the Medical Outcomes Study, and is particularly useful as a generic core with additional disease specific measures of health status. The form is suitable for self-administration in 5 to 10 minutes with a high degree of acceptability and data quality. 8 scales form 2 distinct higher ordered summary measures of physical and mental health (Physical Component Summary (PCS) and Mental Component Summary (MCS) measures). 85% of the reliable variance in the 8 scales is represented in the summary measures. This reduces the number of statistical comparisons involved in analysing the SF-36 without substantial loss of information. Reliability estimates for physical and mental summary scores usually exceed 0.90. The content, construction and predictive validity has been proven in numerous studies. The minimal important difference to standard deviation ratio is relatively high (standardised difference) producing a small sample size.[279,280]

b) Chronic Respiratory Questionnaire

The interviewer led CRQ was the first instrument developed to measure quality of life in patients with COPD. The self-reported CRQ was developed in conjunction with the original author.[281] The overall score is derived from 20 items. Answers are scored on a 7 point scale ranging from 1 (maximum impairment) to 7 (no impairment). Questions are divided into four component domains, namely

'Dyspnoea' (5 items), 'Fatigue' (4 items), 'Emotional Function' (7 items) and 'Mastery' (4 items). A lower score in each dimension reflects a greater degree of dysfunction. Questions covering the domains of fatigue, emotional function and mastery are standardised. The dyspnoea domain is 'individualised' by the patient identifying 5 everyday activities causing the greatest shortness of breath, so each patient has a unique list of activities. The patient selects activities causing breathlessness from a list on the questionnaire, or may volunteer additional activities. Dyspnoea is rated on these self-selected activities at baseline and during subsequent administrations of the CRQ on a 7 point scale ranging from 1 (extremely short of breath) to 7 (not at all short of breath). The entire questionnaire takes approximately 10 minutes to complete. Results are expressed as the mean score for each domain and the mean overall score. Numerous studies have demonstrated reproducibility and responsiveness.[278,281-286]

c) Minnesota Living With Heart Failure Questionnaire

The self-administered MLHFQ consists of 21 questions assessing the patient's perception of heart failure impairing their emotional or physical state. The effects of heart failure on physical, emotional, social and mental dimensions of quality of life are assessed.[287,288] Each question employs a stable 6 point Likert scale from zero (no impairment) to five (severe impairment). The sum of responses reflects the overall severity of heart failure. A relatively low standardised difference produces a large sample size. A change of 7 points is considered clinically meaningful.

2.2.6 Peak expiratory flow

Patients were instructed and observed while using the peak flow meter. The maximum of three technically satisfactory measurements was utilised. Baseline peak expiratory flow (PEF) was measured on the first study day prior to administration of β-blocker. Subsequent measurements were made hourly following administration of study medication.

2.2.7 Spirometry

Spirometry and lung volumes were measured using body plethysmography (Sensormedics, V6200 Autobox, California, USA) 3 hours after administration of study medication and at least 12 hours after inhaled bronchodilators. The variables measured were FEV_1, vital capacity (VC), residual volume (RV), total lung capacity (TLC), specific airways resistance, and specific airways conductance. Tests were performed by the same investigator according to the American Thoracic Society / European Respiratory Society (ATS/ERS) guidelines.[289] The maximum of at least three technically satisfactory and reproducible manoeuvres with less than 10% variation in FEV_1 were accepted. Significant reversibility was defined as greater than 12% increase in FEV_1 15 minutes after inhalation of 400 μg of salbutamol, in agreement with ATS/ERS guidelines.[43] Values were corrected for body temperature, ambient pressure and water saturation. Normal values were determined using the regression equations derived from the European coal and mineworkers' database, including height, age and sex as independent variables.[290]

2.2.8 Transfer coefficient

Diffusing capacity of the lung for carbon monoxide (DLCO) was quantified with the single breath technique using the Transflow System (Morgan Medical) corrected for haemoglobin concentration. Carbon monoxide transfer coefficient (KCO) was calculated from DLCO adjusting for lung volume.

2.3 Study medication

2.3.1 Description

- Generic name bisoprolol fumarate.
- Proprietary name Cardicor.
- Anatomical Therapeutic Chemical classification system ATC Code: C07AB07.
- Active substance bisoprolol fumarate.
- Legal status POM.
- Principle characteristic β_1-selective adrenoceptor blocking agent.
- Dosage 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg, 10 mg.
- Form film-coated tablet.
- Frequency once daily.
- Route oral.
- Manufacturer Merck Pharmaceuticals.
- Marketing authorisation number: PL 00493/0179 – 84.
- Blister container of a polyvinylchloride base film and an aluminium cover foil.
- Chemical name (±)-1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxyl-3-[(1-methylethyl)amino]-2-propanol(E)-2-butenedloate (2:1) (salt).

- Empirical formula $(C_{18}H_{31}NO_4)_2 \bullet C_4H_4O_4$.
- Structure asymmetric carbon atom, racemic mixture, S(-) enantiomer is responsible for most of the β-blocking activity.
- Molecular Weight 766.97.
- White crystalline powder.
- Approximately equally hydrophilic and lipophilic.

2.3.2 Administration

Merck Pharmaceuticals supplied bisoprolol and matching placebo. Packaging, labelling and dispensing of all study medication was performed by Glasgow Royal Infirmary Pharmacy in compliance with local regulations. Eligible consenting patients were assigned in equal proportions to receive bisoprolol or placebo according to a computer generated randomisation list. Bisoprolol was administered under supervision as coded identical tablets containing either bisoprolol or matching placebo. The starting dose of 1.25 mg once daily was increased successively to 2.5 mg, 5.0 mg, 7.5 mg, and 10 mg according to tolerance. Patients were instructed to take one tablet every morning with water without chewing or crushing. A temporary dose down titration was permitted at any time in the event of an intolerable side effect believed to relate to study medication. Subjects were re-challenged at a higher dose once clinically acceptable.

2.3.3 Compliance

Medication compliance was evaluated by the number of pills prescribed compared to the number of pills ingested as reported by the subject and confirmed by

counting the number of pills returned at each attendance. Patients were reinstructed on correct medication usage if compliance was below 80% or above 120%.

2.3.4 Concomitant medication

The following concomitant medication were recorded in checkbox fashion in the electronic CRF: short-acting β_2-agonist, long-acting β_2-agonist, short-acting antimuscarinic, long-acting antimuscarinic, standard-dose corticosteroid, high-dose corticosteroid, modified-release oral theophylline, leukotriene receptor antagonist, nebulised short-acting β_2-agonist, nebulised anticholinergic, oral corticosteroid, aspirin, clopidogrel, warfarin, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, digoxin, amiodarone, aldosterone blockers, statin.

2.3.5 Prohibited medication

Use of the following medications was prohibited in subjects entering the study and during the course of the study: non-dihydropyridine (diltiazem / verapamil) calcium channel blockers, clonidine, monoamineoxidase inhibitors, class-I antiarrhythmic drugs e.g. disopyramide, quinidine, parasympathomimetic drugs, alternative β-blockers, ergotamine derivatives, barbiturates, mefloquine, any investigative trial drug previous one month, previously documented hypersensitivity to bisoprolol or any excipients.

2.3.6 Safety

The sponsor's reporting requirements under the EU Clinical Trials Directive are set out in the European Commission document, 'Detailed guidance on the

collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use' (ENTR/CT3 revision 1, April 2004). The guidance describes requirements for reporting both to the competent authority and the ethics committee in each member state. In the UK, the competent authority is the MHRA and the ethics committee is the research ethics committee (REC) which gave a favourable opinion of the research. Safety reports may be submitted by the sponsor, or by the sponsor's representative, or by the chief investigator.

2.3.7 Suspected unexpected serious adverse reactions

The Medicines for Human Use (Clinical Trials) Regulations 2004 define an 'adverse reaction' as any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject. An adverse reaction is 'unexpected' if its nature and severity are not consistent with the information about the medicinal product in question set out in the case of a product with a marketing authorisation, in the summary of product characteristics for that product. All Suspected Unexpected Serious Adverse Reactions (SUSARS) would be reported to the following three institutions.

a) North Glasgow University Hospitals Division.
b) Medicines and Healthcare products Regulatory.
c) Local Research Ethics Committee.

2.3.8 Expected serious adverse events

An adverse reaction is 'serious' if it results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect. There was no routine requirement to report serious adverse events (SAEs) other than SUSARs.

All acute hospital admissions were reviewed and discussed with the receiving physician. The aim was to continue the current study dose during an exacerbation of HF or COPD with a concurrent increase in appropriate therapy e.g. bronchodilators, diuretics. The following services were considered non-serious: accident and emergency or casualty visits, outpatient and ambulatory procedures, day and short-stay units, rehabilitation facilities, hospice facilities, respire care, nursing homes, custodial care facilities, general practitioner visits.

2.3.9 Adverse Drug Reactions

The following adverse drug reactions were defined.

a) Common (≥1% and <10%)

- feeling of coldness or numbness in the extremities.
- tiredness, exhaustion.
- dizziness.
- headache.
- nausea, vomiting, diarrhoea, constipation.

b) Uncommon (≥0.1% and <1%)

- muscular weakness and cramps.
- bradycardia, AV disturbances.
- worsening of heart failure.
- orthostatic hypotension.
- sleep disturbances.
- depression.
- bronchospasm.

c) Rare (≥0.01% and <0.1%)

- nightmares, hallucinations.
- hypersensitivity reactions (itching, flush, rash).
- increased liver enzymes (ALT, AST), hepatitis.
- increased triglycerides.
- potency disorders.
- hearing impairment.
- allergic rhinitis.
- dry eyes, conjunctivitis.
- provoke or worsen psoriasis or induce psoriasis-like rash.
- alopecia.

2.3.10 Discontinuations

A discontinuation was defined by an enrolled subject ceasing participation in the study prior to completion of the protocol. The primary reason for discontinuation was recorded in the CRF and appropriate follow-up arranged for the patient.

2.4 Ethical considerations

2.4.1 Good clinical practice

The study was conducted in compliance with accepted standards of the International Conference on Harmonisation Good Clinical Practice guidelines, and conformed with all national and local laws, rules and regulations relating to clinical study conduct. The protocol was approved by the local hospital Research Ethics Committee via the Central Office for Research Ethics Committees.

2.4.2 Informed consent

During the screening visit an unambiguous written patient information sheet in simple language was provided, with sufficient time to fully read this information. The study was then discussed in greater detail, allowing for specific questions and providing additional information regarding the study. Each potential subject was adequately informed of the aims, methods, anticipated benefits and potential risks of the study and any discomfort it may entail. Patients were informed of their liberty to abstain from participation in the study and freedom to withdraw consent to participation at any time. Those who agree to participate in the study were invited to attend the Respiratory Function Laboratory at Glasgow Royal Infirmary on a later

date and to read the patient information sheet again at home in the interim. Freely given written informed consent was obtained from all subjects before enrolment.

2.4.3 Confidentiality

Patients were assigned an individual participant number immediately after providing written informed consent. All electronic documents pertaining to personal data, study protocol and results were stored securely by the investigator on home and laptop personal computers, solely accessible by the investigator.

2.4.4 Monitoring

Continuous monitoring was undertaken throughout by supervisors Dr FG Dunn, Dr G Chalmers and Dr R Carter. The study was subject to review at any time by the West Glasgow Local Research Ethics Committee.

2.4.5 Amendments

A notice of amendment was submitted to the Research Ethics Committee and the Medicines and Healthcare products Regulatory Agency in the event of any substantial amendment to the Clinical Trial Authorisation, study protocol, or supporting documentation. A substantial amendment was defined as any amendment that is likely to affect to a significant degree: the safety or physical or mental integrity of the trial participants, the scientific value of the trial, the conduct or management of the trial, the quality or safety of any investigational medicinal product used in the trial.

2.4.6 Sponsor

North Glasgow University Hospitals Division served as trial sponsor.

2.4.7 Registration numbers

ClinicalTrials.gov, number: NCT00702156

European Clinical Trials Database (EudraCT) Number: 2004-005152-14

REC reference number: 05/S0709/2

2.5 Recruitment

2.5.1 Methods

Patients suitable to participate in the study were contacted initially by telephone or in person during the hospital admission or out-patient department visit. The nature of the study was verbally explained and patients were asked if they were interested in participating. Those expressing an interest were invited to attend for a screening visit.

Study participants were identified by screening of patients within a single domain (North Glasgow University Hospitals Division) at three hospital sites (Stobhill Hospital, Royal Infirmary, Western Infirmary). Screening sources included the heart failure nurse led service database, cardiology out-patient clinics, emergency or elective admissions to the cardiology or general medical wards, and correspondence relating to outpatient clinics and hospital discharges.

Numerous strategies were employed to improve recruitment. Additional sites were added through major protocol amendments, including the Victoria Infirmary. Patients attending the transplant unit and chest clinics were screened. The study outline and enrolment criteria were presented to groups involved in the care of potential patients. These were followed up using written material, emails, phone calls and personal visits. Posters and information leaflets were provided in the relevant clinical areas.

2.5.2 Limitations

Recruitment was challenging for numerous reasons. Surprisingly few patients had moderate to severe airflow obstruction. Many had only mild airflow obstruction or were misdiagnosed with COPD. Similarly, patients were unsuitable due to misdiagnosis of HF, isolated right heart failure, or heart failure with preserved ejection fraction. Many patients with COPD were already prescribed β-blockers. β-blockers were often contraindicated or considered inappropriate for reasons other than COPD. These included atrioventricular block, bradycardia, hypotension, asthma, dementia, poor compliance, advanced malignancy and palliative care. Diltiazem use was surprisingly common and difficult to substitute with study medicine that may be placebo. Physical incapacity, extensive comorbidities and reluctance to visit hospital were problematic in this elderly population. Finally, patients with HF and COPD had significant symptoms and were reluctant to participate in a trial, particularly during the winter months.

Chapter 3

Bisoprolol in patients with heart failure and moderate to severe chronic obstructive pulmonary disease; a randomised controlled trial.

3.1 Introduction

Heart failure and chronic obstructive pulmonary disease are global epidemics, each affecting in excess of ten million patients.[4,5] The combination presents many diagnostic and therapeutic dilemmas.[1] International guidelines are clear in defining the unequivocal morbidity and mortality benefits of β-blockade in patients with HF.[4,158] They are less clear in defining when, or indeed whether, β-blockers should be avoided in patients with COPD (with or without reversible airflow obstruction). Pulmonary disease was the most powerful independent predictor of β-blocker underutilisation in the Euro Heart Failure Survey (odds ratio 0.35 [95% CI 0.30 – 0.40]).[173] Concerns stem from reports of acute bronchospasm in asthmatic patients given non-cardioselective β-blockers.[161-163] No study has prospectively examined β-blockade tolerability and efficacy in populations with both HF and COPD. The evidence derives from those with COPD alone. We conducted a randomised, double-blind, placebo controlled study examining the effect of bisoprolol on pulmonary function and quality of life in patients with HF and coexistent moderate to severe COPD.

3.2 Methods

3.2.1 Study design

The primary research objective was to demonstrate that cardioselective β-blockade using bisoprolol was not inferior to placebo with regard to pulmonary function in patients with HF and coexistent moderate to severe COPD with or

without significant reversibility. Secondary outcomes included health status, dyspnoea ratings and arterial gases. The study was approved by the regional ethics committee and all patients provided written informed consent. Patients were prospectively randomised in equal proportions and double-blind manner to receive bisoprolol or matching placebo. A sample size of 126 was estimated to provide 80% power (α=0.05) to detect equivalent pulmonary function (difference FEV_1 less than 0.2 litres), assuming a standard deviation of 0.45 litres. The study is registered with ClinicalTrials.gov, number: NCT00702156. Recruitment commenced in March 2005 and was terminated in July 2008 after limited enrolment.

3.2.2 Entry criteria

The principal inclusion criteria were: 1) stable symptomatic HF; 2) LVEF < 40% by echocardiography or radionuclide ventriculography; 3) moderate or severe COPD defined by the Global Initiative for Chronic Obstructive Lung Disease criteria (Table 1.1); 4) a minimum 10 pack year smoking history. Reversible airflow obstruction was not an exclusion criteria, unless in conjunction with pre-existing asthma.

The principal exclusion criteria included standard contraindications to β-blocker therapy: atrioventricular block greater than first degree without a pacemaker; bradycardia less than 60 beats per minute, systolic blood pressure less than 100 mmHg; acute heart failure or cardiogenic shock; peripheral arterial disease with symptoms at rest; and standard clinical criteria of asthma including young age of symptom onset or response to provocative stimuli. Concurrent treatment with non-

dihydropyridine calcium channel blockers, antiarrhythmic drugs other than amiodarone and digitalis, and alternative β-blockers was not permitted.

3.2.3 Protocol

Patients attended one baseline and initiation visit (Day 0) and 5 follow up visits over 4 months (Weeks 2, 4, 8, 12, 16). Medication was administered under supervision. The starting dose of 1.25 mg once daily was increased successively to 2.5 mg, 5.0 mg, 7.5 mg, and 10 mg according to tolerance. In patients with worsening HF, baseline therapy was increased before the study drug was decreased. Each visit included evaluation of symptoms, physical signs, pulse oximetry, health status, peak expiratory flow, spirometry and body plethysmography. All patients were clinically euvolaemic at the time of pulmonary function testing. Carbon monoxide transfer factor, electrocardiography and arterialised earlobe capillary blood gases were performed at study onset and completion. Health status was assessed using one generic and two disease specific instruments at each visit: the Short Form 36, Chronic Respiratory Questionnaire and the Minnesota Living with Heart Failure Questionnaire.[278]

3.2.4 Pulmonary function tests

Spirometry and lung volumes were measured using body plethysmography (Sensormedics, V6200 Autobox, California, USA) 3 hours after administration of study medication and at least 12 hours after inhaled bronchodilators. The variables measured were FEV_1, vital capacity, residual volume, total lung capacity, specific airways resistance, and specific airways conductance. Diffusing capacity of the lung

for carbon monoxide was quantified with the single breath technique using the Transflow System (Morgan Medical) corrected for haemoglobin concentration. Carbon monoxide transfer coefficient was calculated from DLCO adjusting for lung volume. Tests were performed by the same investigator according to the American Thoracic Society / European Respiratory Society (ATS/ERS) guidelines.[289] The maximum of at least three technically satisfactory and reproducible manoeuvres with less than 10% variation in FEV_1 were accepted. Significant reversibility was defined as greater than 12% increase in FEV_1 15 minutes after inhalation of 400 µg of salbutamol, in agreement with ATS/ERS guidelines.[43] Values were corrected for body temperature, ambient pressure and water saturation. Normal values were determined using the regression equations derived from the European coal and mineworkers' database, including height, age and sex as independent variables.[290]

3.2.5 Statistical analysis

Baseline characteristics of patients are presented as means with standard deviations for continuous variables or by frequencies and percents for categorical variables. The data were assessed for normality using the Shapiro-Wilk's test. Means were compared using the Wilcoxon rank sum test or Student t-test (with Levene's test for equality of variances) depending on the distribution of the data. Proportions were compared using the Chi-square test, or Fisher's Exact test when the observed frequencies were less than five. A 2-tailed P value of less than 0.05 was considered statistically significant. All analyses were performed on an intention to treat basis. Pulmonary function and quality of life scores were analysed as change

from baseline to the final visit, comparing bisoprolol and placebo groups. Statistical analyses were performed using SPSS Version 13 (SPSS Inc., Chicago, Illinois).

3.3 Results

3.3.1 Recruitment

458 patients with a case record diagnosis of HF and COPD were identified. Of these, 27 patients were enrolled. The remainder were excluded for the following reasons: existing β-blocker therapy (n=144), no airflow obstruction on spirometric testing (n=43), heart failure with preserved ejection fraction (n=36), mild airflow obstruction (n=27), concurrent diltiazem (n=26), declined participation (n=24), asthma (n=22), physical incapacity (n=22), heart failure secondary to valvular heart disease (n=18), cancer or receiving palliative care (n=16), hypotension (n=11), bradycardia (n=9), dementia (n=9), poor compliance (n=8), cor pulmonale with preserved left ventricular systolic function (n=6), very severe airflow obstruction (n=6), and atrioventricular block (n=4).

3.3.2 Baseline Characteristics and Titration

The baseline characteristics of each group were comparable (Table 3.1). Patients were elderly (mean age 70.8 ± 9.1 years) and predominantly male. Cardiovascular comorbidity and smoking history were similar in the two groups (48.6 vs 43.4 pack years, p=0.64). All patients were receiving treatment with either angiotensin converting enzyme inhibitors or angiotensin receptor blockers, diuretics

and inhaled β-agonists. Resting heart rates were alike, but blood pressure was greater in the bisoprolol group (129/69 vs 117/63, p=0.02).

Table 3.1 Baseline characteristics and details of bisoprolol titration

mean ± SD or n (%)	Bisoprolol n=14	Placebo n=13
Demographics		
Age (years)	72.8 ± 7.4	68.7 ± 10.6
Male Sex	9 (64)	10 (77)
Body Mass Index	29.2 ± 5.6	26.9 ± 4.4
Smoking History (Pack Years)	48.6 ± 33.3	43.4 ± 22.0
Airflow Obstruction		
FEV_1	1.37 ± 0.42	1.26 ± 0.42
Percent predicted normal value (%)	57 ± 15	50 ± 14
GOLD Moderate	9 (64)	7 (54)
GOLD Severe	5 (36)	6 (46)
Reversibility		
FEV_1 change post salbutamol	0.11 ± 0.08	0.22 ± 0.19
FEV_1 percent reversibility (%)	10.4 ± 10.8	17.9 ± 17.9
Proportion > 12% reversibility	5 (36)	7 (54)
Cardiovascular History		
Ejection Fraction (%)	28.1 ± 5.9	27.1 ± 6.2
Angina	4 (29)	4 (31)
Myocardial infarction	5 (36)	6 (46)
Atrial fibrillation	4 (29)	3 (23)
Medications		
ACEI or angiotensin receptor blocker	14 (100)	13 (100)
Diuretic	14 (100)	13 (100)
Inhaled β-agonist	14 (100)	13 (100)
Inhaled antimuscarinic	6 (43)	8 (62)
Inhaled steroid	9 (64)	10 (77)
Examination		
Heart rate baseline (beats/min)	82.9 ± 15.7	84.5 ± 15.9
Systolic BP (mm Hg)	128.9 ± 14.0*	116.8 ± 9.5

*P<0.05 compared with placebo

Mean baseline FEV_1 was 1.37 L (57% predicted) and 1.26 L (50% predicted) in those receiving bisoprolol and placebo respectively (p=0.52). Similar proportions were classified as having moderate or severe airflow obstruction. Peak expiratory flow rates were also comparable (209 L/min vs 216 L/min respectively). Significant reversibility, defined as >12% increase post salbutamol, was observed in 36% of

patients receiving bisoprolol and 54% of those allocated to placebo (p=NS). Mean baseline residual volume was increased in both groups, consistent with gas trapping secondary to airflow obstruction (respectively 2.85 L vs 3.21 L, 118% vs 138% predicted, p=0.37).

The mean final dose of study medication was 7.3 mg and 8.4 mg in the bisoprolol and placebo groups respectively. Titration was limited by bradycardia in 6 patients receiving β-blockade, but in none receiving placebo (p=0.02). During titration the mean heart rate reduction for bisoprolol compared to placebo was 21.0 beats per minute (p<0.001). This was paralleled by a non-significant decrease in systolic blood pressure of 6.6 mmHg relative to placebo. Two patients in each group withdrew during the course of the study, citing fatigue (bisoprolol), personal reasons (bisoprolol), dyspnoea (placebo) and insomnia (placebo).

3.3.3 Effect of Bisoprolol on Pulmonary Function

A significant reduction in pre-bronchodilator FEV_1 occurred after 4 months following treatment with bisoprolol compared with placebo (–70 ml vs +120 ml, p=0.01). An analogous trend in PEF was observed (–13 L/min vs +12 L/min, p=0.06). Post-bronchodilator FEV_1 was also reduced (respectively –90 ml vs +20 ml, p=0.03). Reversibility following inhaled β_2-agonist was not however significantly impaired by bisoprolol (Table 3.2).

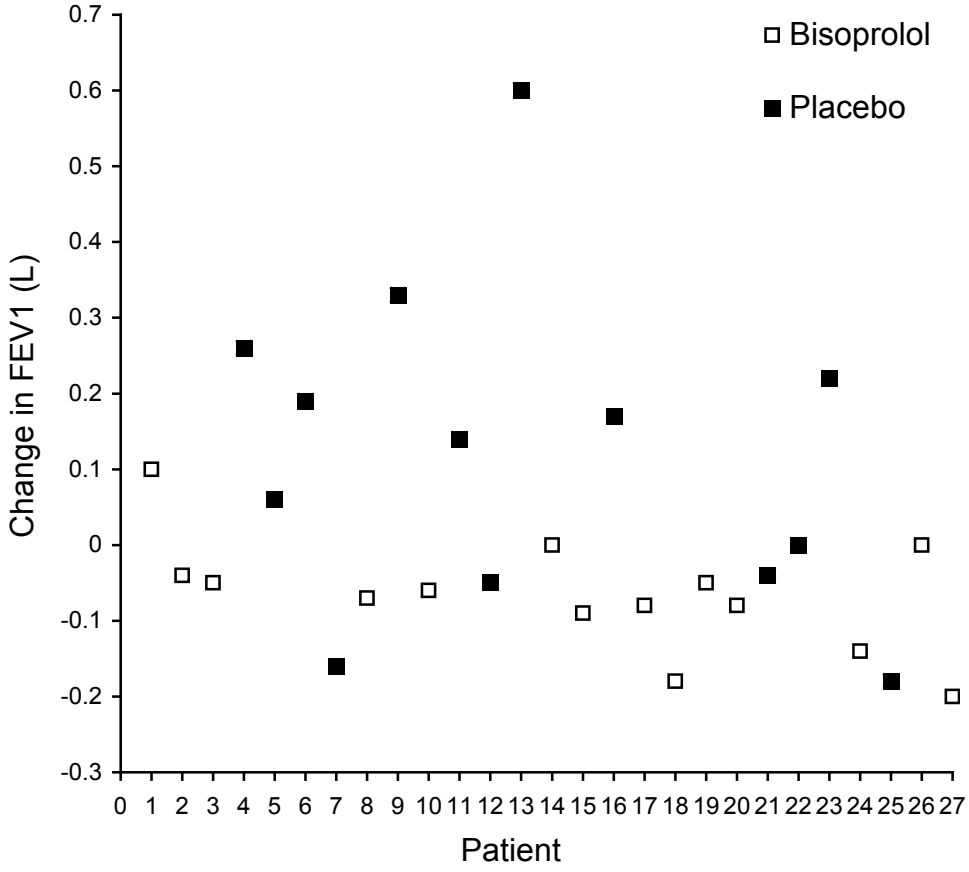
Table 3.2 Effect of bisoprolol on pulmonary function

mean ± SD	Bisoprolol n=14	Placebo n=13
FEV_1 (L)		
Baseline	1.37 ± 0.42	1.26 ± 0.42
Change	-0.07 ± 0.08*	0.12 ± 0.21
FEV_1 Reversibility (L)		
Baseline	0.11 ± 0.08	0.22 ± 0.19
Change	-0.03 ± 0.09	-0.10 ± 0.08
FEV_1 Post Salbutamol (L)		
Baseline	1.48 ± 0.40	1.48 ± 0.50
Change	-0.09 ± 0.10*	0.02 ± 0.15
Peak Expiratory Flow (L/min)		
Baseline	209 ± 60	216 ± 75
Change	-13 ± 17	12 ± 40
Vital Capacity (L)		
Baseline	2.66 ± 0.91	2.56 ± 0.74
Change	-0.07 ± 0.19	0.10 ± 0.30
Residual Volume (L)		
Baseline	2.85 ± 0.94	3.21 ± 1.09
Percent Predicted Normal Value (%)	118 ± 29	138 ± 44
Change	0.06 ± 0.56	-0.04 ± 0.51
Total Lung Capacity (L)		
Baseline	5.51 ± 1.35	5.83 ± 1.25
Change	-0.01 ± 0.57	-0.02 ± 0.54

*P<0.05 compared with placebo

The mean bronchodilator response in those receiving bisoprolol (+90 ml) was of similar magnitude to the reduction in FEV_1 from baseline. Lung volumes including VC and TLC were unaffected. Residual volume, which reflects the degree of air trapping, exhibited no significant change (+60 ml vs –40 ml, p=0.63). Given the small patient numbers, the change in FEV_1 from baseline was examined by scatterplot for consistency and outliers (Figure 3.1). This confirmed an increase in airflow obstruction in most patients.

Figure 3.1 Mean change in forced expiratory volume with bisoprolol



3.3.4 Health Status

All measures of health status exhibited non-significant trends to improvement in patients receiving bisoprolol (Table 3.3). The SF-36 physical and mental component scores both increased relative to placebo (2.6 vs 0.5 and 0.8 vs –0.3 respectively). Similarly, the MLHFQ score decreased (–2.5 vs 3.5) and CRQ total increased (0.07 vs –0.24), both indicating improvement. Finally, the CRQ component score examining dyspnoea also increased (0.51 vs –0.14). The mean number of exacerbations of COPD during the study was similar in the bisoprolol and placebo groups (respectively 0.50 and 0.31, p=0.44).

Table 3.3 Effect of bisoprolol on health status*

mean ± SD	Bisoprolol n=14	Placebo n=13
SF-36 PCS		
Baseline	31.7 ± 7.5	32.6 ± 8.1
Change	2.6 ± 5.4	0.5 ± 4.5
SF-36 MCS		
Baseline	42.3 ± 9.9	38.6 ± 11.8
Change	0.8 ± 6.0	-0.3 ± 9.5
MLHFQ		
Baseline	49.4 ± 25.5	47.4 ± 21.0
Change	-2.5 ± 12.3	3.5 ± 11.1
CRQ Total		
Baseline	3.94 ± 0.85	3.75 ± 0.95
Change	0.07 ± 0.64	-0.24 ± 0.68
CRQ Dyspnoea		
Baseline	2.57 ± 0.81	3.08 ± 1.22
Change	0.51 ± 1.19	-0.14 ± 1.27

* For all scales, except MLHFQ, a positive change equates to an improvement; for MLHFQ, a negative change equates to improvement. SF-36 = Short Form 36; PCS = physical component score; MCS = mental component score; MLHFQ = Minnesota Living with Heart Failure Questionnaire; CRQ = Chronic Respiratory Questionnaire

3.3.5 Arterial blood gases and diffusing capacity of lung

Baseline blood gases revealed significant hypoxaemia (Table 3.4). Mean resting partial pressure of oxygen (PaO_2) was similar in the bisoprolol and placebo groups (9.49 vs 8.83, p=0.09). Resting partial pressure of carbon dioxide ($PaCO_2$) was also comparable (5.10 vs 5.48, p=0.09). No significant change occurred in PaO_2, $PaCO_2$ or oxygen saturation following treatment with bisoprolol as compared to placebo. Baseline transfer coefficient was impaired in both groups, respectively 58% and 54% of predicted normal values. A significant reduction in transfer coefficient was observed in those receiving bisoprolol relative to placebo (-0.33 mmol/min/kPa/l vs 0.17 mmol/min/kPa/l, p=0.01).

Table 3.4 Effect of bisoprolol on transfer coefficient and blood gases

mean ± SD	Bisoprolol n=14	Placebo n=13
Transfer coefficient (mmol/min/kPa/l)		
Baseline	4.49 ± 1.52	4.36 ± 1.60
Percent Predicted Normal Value (%)	58 ± 19	54 ± 15
Change	-0.33 ± 0.45*	0.17 ± 0.50
PaO_2 (kPa)		
Baseline	9.49 ± 0.90	8.83 ± 1.00
Change	-0.30 ± 0.85	0.26 ± 1.27
$PaCO_2$ (kPa)		
Baseline	5.10 ± 0.29	5.48 ± 0.70
Change	0.10 ± 0.36	-0.15 ± 0.63
SaO_2 (%)		
Baseline	95.6 ± 1.45*	93.5 ± 3.27
Change	-0.55 ± 1.61	0.12 ± 3.71

*P<0.05 compared with placebo

PaO_2 = partial pressure of oxygen; $PaCO_2$ = partial pressure of carbon dioxide; SaO_2 = oxygen saturation

3.4 Discussion

This is the first randomised controlled study to examine the effect of β-blockade in patients with heart failure and concurrent COPD. An especially challenging group of patients with heart failure was selected to study the effects of bisoprolol: those with moderate or severe COPD with and without reversibility, who physicians had thus far not considered candidates for β-blockers. Participants exhibited significant airflow obstruction (mean FEV_1 1.32 L) akin to previous studies in moderate to severe COPD.[194,196,198,276,291] The mean dose (7.3 mg) and heart rate reduction (21.0 bpm) compare favourably with the CIBIS II trial (7.5 mg and 9.8 bpm).[292] The study has the longest follow up period of any placebo controlled trial of β-blockade in COPD, and additionally reports the impact on quality of life. Several key findings emerged. Treatment with bisoprolol was associated with an

increase in airflow obstruction. Bronchodilator response to inhaled β_2-agonist was preserved. While baseline health status was significantly impaired, β-blockade exerted no adverse effect on health related quality of life or functional status.

A Cochrane Library meta-analysis concluded that long term cardioselective β-blockade is safe and well tolerated in COPD.[2,180] This evaluated pulmonary function in 20 randomised, controlled trials of cardioselective β-blockers in patients with COPD. The available evidence has major limitations. Only two studies involved greater than 20 patients,[192,198] two were single rather than double-blinded,[196,197] and others lacked placebo controls.[182,192,193,196] Not one study included patients with HF. Eleven trials involved single doses and only one lasted longer than a month.[192] The effect of long term β-blockade is therefore largely unknown. Information is particularly limited for β-blockers conferring benefit in HF: only two single dose studies used bisoprolol,[190,191] and none carvedilol. The present report in part addresses these shortcomings.

The FEV_1 response to bisoprolol was consistent with existing evidence. The Cochrane analysis observed no significant change in FEV_1 with longer term cardioselective β-blockade (–2.39% [CI –5.69% to 0.91%]).[2] However, the trials included in the meta-analysis exhibited a degree of heterogeneity. In the longest study of patients with severe COPD, atenolol and metoprolol each significantly reduced FEV_1 by around 10% over four weeks.[195] I observed a reduction in FEV_1 of similar magnitude (post-bronchodilator 110 ml, 7%). The two prior randomised controlled studies of bisoprolol administered only single doses in patients with mild to moderate COPD.[190,191] The bronchodilator response to the inhaled β_2-agonist

salbutamol was unaffected. The present study corroborates these findings in more severe airflow obstruction over longer term follow up.

The findings have sound physiological rationale. Bronchodilatation is mediated by autonomic muscarinic cholinoceptors and β adrenoceptors, the dominant subtypes being M_3 and β_2 respectively.[293] B-blocker cardioselectivity is dose dependent, with competitive antagonism of both β_1 and β_2-adrenoceptors occurring at higher plasma concentrations.[175,294-296] With higher doses of cardioselective β-blockers, β_2 receptor blockade may cause minor increases in airflow obstruction in susceptible patients,[201,294-296] possibly through unopposed parasympathetic bronchoconstriction.[293,297] Bisoprolol is highly β_1-selective, providing a wide split between β_1 and β_2-adrenoceptor blockade.[175,190,191,295,296,298] At therapeutic levels, response to β_2-agonists remains largely preserved and counteracts any change in airway resistance.[190,191,294,296,299]

Patients with HF or COPD have a high symptom burden which is often overlooked by traditional assessments.[300] No previous study has formally assessed health status or symptoms in patients with both conditions. The mean baseline scores all indicated worse health status than in two contemporary studies involving 50 and 30 patients with heart failure: mean MLHFQ 48.4 ± 23.0 (versus 41.8 ± 24.9 and 44.5 ± 26.6); mean SF-36 PCS 32.1 ± 7.7 (versus 33.5 ± 10.7 and 32.8 ± 8.8); mean SF-36 MCS 40.5 ± 10.8 (versus 48.7 ± 10.3 and 46.6 ± 12.0).[280,301] The mean CRQ dyspnoea score of 2.8 ± 1.0 was similar to that in trials of pulmonary rehabilitation involving patients with moderate to severe COPD.[278,286] My results suggest that patients with both HF and COPD have significantly impaired quality of

life. This highlights the need for strategies to detect and improve symptoms as well as prognosis.

To my knowledge, the effect of β-blockade on health status has never been assessed in any cohort with COPD. Many studies only describe dyspnoea of sufficient magnitude to merit voluntary self-reporting. Moderate and less acute symptoms may be inadequately assessed. The perception of respiratory effort and associated distress is subjective and variable with time, reflecting a complex interaction between psychology and physiology.[203] No trial formally graded dyspnoea at baseline and follow-up using validated scales. Furthermore, quantification based on physical exertion also fails to reflect mental health and social functioning.[204] My results are encouraging for three reasons. Most importantly, β-blockade exerted no adverse effect on health related quality of life or functional status. Secondly, all three measures of health status and components including dyspnoea score improved. Though not statistically significant, the consistent directionality of change is reassuring. Finally, the observations are concordant with the stable residual volume, as hyperinflation predicts exercise capacity better than FEV_1.[302]

Resting hypoxaemia reflects the severity of gas exchange impairment and predicts prognosis in patients with COPD.[303] The mean PaO_2 and $PaCO_2$ of my cohort were similar to previous trials in severe airflow obstruction,[195,304] and not significantly influenced by bisoprolol. This corroborates a prior study in 12 patients with severe COPD, in which gas tensions were unaffected by metoprolol over a 4 week period.[195] The reduction in transfer coefficient confirms reports using carvedilol and propranolol.[305,306] However, in a recent study bisoprolol increased

diffusing capacity of the lung compared to carvedilol in 53 patients with HF.[299] This was attributed to changes in membrane conductance relating to regulation of alveolar fluid balance mediated by β_2-receptors. Differences in population and study design may explain the disparity. Lung diffusing capacity depends on ventilation, membrane conductance and capillary blood volume. My patients had significant airflow obstruction (mean FEV_1 1.32 L vs 2.71 L) and received higher doses of bisoprolol (7.3 mg vs 4.8 mg) than in the aforementioned study. I also compared bisoprolol to placebo as opposed to carvedilol, which reduces DLCO in patients with HF.[305]

Several shortcomings must be acknowledged, foremost being the limited recruitment. Many patients tolerated β-blockers, had preserved ejection fraction, or only mild airflow obstruction. β-blockers were often contraindicated or considered inappropriate for reasons other than COPD. Finally, physical incapacity and reluctance to visit hospital were problematic in this elderly population. This information should prove useful when planning future β-blocker trials in patients with HF and COPD. The limited numbers increase the risk of type II statistical error, namely of missing a real difference. For example, the current sample size provides 63% power to detect a reduction in mean SF-36 PCS of 6.0 (the accepted minimal important difference) using the observed standard deviation of 7.7. The advanced age and comorbidity of patients prohibited cardiopulmonary exercise testing. Assessment of oxygen consumption, anaerobic threshold and ventilatory response would improve our understanding of the exertional impairment that characterises this patient cohort. Finally, measurement of diffusion components using the Roughton

and Forster method was not included in the protocol to reduce patient burden. The mechanism of reduction in diffusing capacity is therefore uncertain.

3.5 Conclusion

Patients with HF and COPD represent a large and often ignored population. For the first time, I have prospectively examined the controversial issue of β-blockade in patients with both conditions. A significant reduction in FEV_1 was observed following treatment with bisoprolol. No reduction in quality of life accompanied this change. These findings pose crucial questions and provide direction for larger randomised controlled trials. Is an asymptomatic reduction in FEV_1 an acceptable sacrifice given the established prognostic benefits of β-blockers? Will symptoms and quality of life improve significantly over longer follow up? Are the effects of β-blockade on airflow obstruction and reversibility dose dependent? Would combining long acting β-agonist and antimuscarinic therapy offset the effects of β-blockade? Robust clinical trials are required to provide the answers which may finally allay physicians' mistrust of β-blockers in patients with COPD.

Chapter 4

Primary care burden and treatment of patients with heart failure and chronic obstructive pulmonary disease in Scotland.

4.1 Introduction

Heart failure is an important public health problem in industrialised countries with ageing populations.[88,307] Chronic obstructive pulmonary disease is among the commonest reasons for consulting a general practitioner and frequently coexists with heart failure.[88] Both conditions are increasing in prevalence and present significant challenges to healthcare providers.[4,308,309] Few reports have addressed this often ignored combined presentation of disease,[61] and fewer still the consequences of both conditions co-existing in the community.[137] In randomised controlled trials, many drugs confer significant morbidity and mortality benefits in patients with HF: angiotensin converting enzyme inhibitors, β-blockers, spironolactone and angiotensin receptor blockers. Uptake of these advancements into routine clinical care has been limited.[88] Concurrent COPD is often cited as an obstacle to implementing β-blockers.[310]

To further understand the relationship between these two conditions, this study examines the incidence and prevalence of COPD in patients with HF in Scotland. The study focuses on temporal trends, age related variation, and socioeconomic differences. Finally, the comorbid diagnoses and prescribed treatments in patients with and without COPD are described.

4.2 Methods

In Scotland every citizen receives free primary care through the National Health Service, and all patients receiving emergency hospital care are discharged

back to the care of their general practitioner (GP). All prescriptions are provided via primary care, with the exception of a short supply of drugs provided by hospitals immediately after a patient is discharged from hospital. Subsequent repeat prescriptions are provided through primary care, as are those for treatments recommended during hospital clinic visits. The continuous morbidity recording (CMR) scheme prospectively collects detailed information from primary care practices.[88,311] Practices are weighted to form a national sample that is broadly representative of the whole population in terms of age, sex, socioeconomic status and rural-urban mix.[311] By 2004, 61 practices with 377,439 patients (covering approximately 7% of the Scottish population) had participated in the CMR and contributed data to the Primary Care Clinical Informatics Unit at the University of Aberdeen. The scheme allows accurate estimates of the national prevalence, incidence, consultation rates, concomitant medical problems and drug treatment for patients with heart failure in primary care.[88]

Practices participating in the CMR scheme record every face to face contact between patients and doctors (including temporary residents and locum doctors). For each contact doctors may record up to 10 problems, describing each as specifically as possible in diagnostic terms. Each diagnosis is assigned a Read code and 'modifier' of 'first', 'recurrent' or 'persistent' to denote whether the problem is new, recurrence of a previous problem or a continuing problem, respectively. Details of drugs prescribed and repeat prescriptions are also recorded. A quality assurance programme of rolling practice visits compares CMR data with practice held records.

From 1 April 1999 to 31 March 2004, all patients diagnosed with HF (Read codes: G58.. and below, G34y., G34y1 and G34y2) or COPD (H3…, H31.. and

below (excluding H3101, H31y0, H3122), H32.. and below, and H36.. to H3z..) were identified. The period prevalence for each condition was estimated using the alternate condition as denominator. The incidence was estimated by including all patients with a Read code modifier of 'first'. Contact rates were determined as the total number of consultations involving that condition ('contacts') over the year. Indirect standardisation was used to adjust incidence, prevalence and contact rates for age and sex differences in the practice population.[312] Individuals were assigned a Carstairs deprivation category (a validated measure of socioeconomic status) from one (least deprived) to five (most deprived) based on postcodes of residence.[313] These categories are derived from 1991 census data on the proportion of residents who are unemployed, occupy overcrowded accommodation, lack a car, or belong to a low occupational social class.

Comorbidity and prescribing data were compared in patients with and without COPD. A two-tailed P value of less than 0.05 was considered statistically significant. Chi square tests, z tests and exact tests were used where appropriate for categorical data, proportions and means. Logistic regression was used to determine factors associated with the prescription of β-blockers. Variables were entered into the model based on clinical relevance and published predictors of β-blocker use. The final model included the following covariates: age, sex, year, and presence of COPD, angina, previous myocardial infarction, atrial fibrillation and hypertension. Age was treated as a continuous variable. Adjusted odds ratios and 95% confidence intervals were calculated. All analyses were performed using SPSS for Windows v16.0 (SPSS Inc., Chicago, Illinois).

4.3 Results

4.3.1 Prevalence of HF and COPD in the general population

The crude prevalence of clinically reported HF in the CMR population increased from 1.31% in 1999 to 1.55% in 2002, but appeared to plateau thereafter. By contrast, the prevalence of COPD increased every year rising from 2.35% to 3.10% in 2004 (p for trend <0.001), becoming nearly twice as prevalent as HF.

4.3.2 Prevalence of COPD in patients with HF

As in the general population, the crude prevalence of COPD in patients with HF increased every year between 1999 and 2004, from 19.8% to 23.8% (Table 4.1). The age standardised prevalence also rose over this period (p=0.003).

Table 4.1 Prevalence and incidence of COPD (per 100 population with HF), stratified by year

Year	CMR Population	Prevalence of HF (n)	Prevalence of COPD (n)	Prevalence of COPD in HF patients (n)	Age standardised prevalence of COPD in HF patients	Incidence of COPD in HF patients (n)	Age standardised incidence of COPD in HF patients
1999	354041	1.31 (4628)	2.35 (8309)	19.8 (916)	9.7	1.6 (73)	0.3
2000	376085	1.40 (5253)	2.51 (9447)	20.5 (1078)	9.9	1.2 (63)	0.3
2001	375916	1.49 (5590)	2.70 (10162)	21.8 (1217)	11.8	1.3 (71)	0.3
2002	375280	1.55 (5829)	2.89 (10853)	22.9 (1333)	12.6	1.2 (68)	0.7
2003	372967	1.56 (5826)	3.00 (11188)	23.6 (1375)	13.9	1.3 (75)	0.7
2004	374893	1.56 (5834)	3.10 (11631)	23.8 (1389)	13.5	1.3 (77)	0.9
p for trend		0.007	<0.001	0.001	0.003	0.340	0.017

Age, gender and socioeconomic differences were examined in the most recent year, 2004 (Tables 4.2 and 4.3). The prevalence of COPD was similar in men and women (24.8% vs 22.9%). Prevalence was lowest in younger patients with heart failure (9.4%), rising to around 26% in those aged 55 to 85 years, before declining to

18.0% in those aged over 85 years. The prevalence of COPD increased with greater socioeconomic deprivation rising from 18.6% in the least deprived to 31.3% in the most deprived group (rate ratio 1.27 [95% CI 1.05–1.55], p=0.01). The prevalence of smoking likewise rose from 24.9% to 42.1% in the least and most deprived stratum respectively (p=0.011) (Table 4.3).

Table 4.2 Prevalence, incidence and contact rates for COPD (per 100 population with HF), stratified by age and sex for April 2003 to March 2004

Age and gender	Population with HF	Prevalence of COPD (n)	Incidence of COPD (n)	Contact rate for HF or COPD (n)
Sex				
Male	2732	24.8 (678)	1.8 (48)	69.3 (1893)
Females	3102	22.9 (711)	0.9 (29)	55.5 (1723)
p value		0.090	0.006	<0.001
Age				
< 55	298	9.4 (28)	0.7 (2)	28.9 (86)
55 – 64	693	26.0 (180)	2.2 (15)	63.8 (442)
65 – 74	1648	26.2 (432)	1.4 (23)	66.3 (1093)
75 – 84	2193	25.9 (569)	1.3 (29)	65.3 (1433)
≥ 85	1002	18.0 (180)	0.8 (8)	56.1 (562)
p value for trend		0.55	0.178	0.32

Table 4.3 Prevalence, incidence and contact rates for COPD (per 100 population with HF), stratified by socioeconomic status for April 2003 to March 2004

Deprivation Category	Population with HF	Prevalence of smoking in HF patients (n)	Prevalence of COPD in HF patients (n)	Age standardised prevalence	Incidence of COPD in HF patients (n)	Age standardised incidence	Contact rate for HF or COPD (n)	Age standardised contact rate
1 (least)	902	24.9 (225)	18.6 (168)	18.6	1.1 (10)	1.1	59.0 (532)	58.3
2	1106	23.6 (261)	22.2 (246)	22.0	1.4 (15)	1.4	69.2 (765)	68.4
3	1639	32.7 (536)	24.5 (402)	24.6	1.7 (28)	1.7	66.7 (1094)	66.8
4	1322	33.7 (445)	22.8 (302)	22.8	1.0 (13)	1.0	54.5 (720)	54.7
5 (most)	865	42.1 (364)	31.3 (271)	31.5	1.3 (11)	1.3	58.4 (505)	59.3
Rate Ratio (95% CI)			1.27 (1.05-1.55)	1.63 (0.89-3.06)	1.18 (0.49-2.91)	1.18 (0.49-2.91)	0.98 (0.67-1.43)	1.02 (0.70-1.49)
p value for trend		0.011	0.01	0.05	0.84	0.84	0.92	0.60

4.3.3 Incidence of COPD in patients with HF

The crude incidence of COPD in patients with HF remained relatively stable with a range of 1.2 – 1.6% between 1999 and 2004 (Table 4.1). However, the age standardised incidence increased from 0.3% to 0.9% over this period (p for trend=0.017). Age, sex and socioeconomic differences were again examined in the most recent year (Tables 4.2 and 4.3). The incidence of COPD among men with HF was double that observed in women (1.8% vs 0.9%). As with prevalence, incidence was lowest in the young (under 55 years) and elderly (over 85 years). The incidence was highest in those aged 55 to 64 years (2.2%). No significant difference was observed in the incidence of COPD according to socioeconomic deprivation (p for trend = 0.84), although the number of cases in each category was small.

4.3.4 Contact rates for HF and COPD

The contact rate for HF or COPD in patients with both conditions was greater than the disease specific contact rate in patients with either condition alone (Table 4.4). Between 1999 and 2004 the contact rate for COPD alone was relatively stable (p=0.85). No significant change was observed in the age standardised contact rate for those with both HF and COPD during the same period (p=0.96). By contrast, the contact rate for HF alone more than halved (from 49.7 to 23.5 per 100 population with HF, p=0.011). Age, sex and socioeconomic differences were examined in 2003-4 (Tables 4.2 and 4.3). The contact rate for HF or COPD was lower in women than in men, and in the young (< 55 years) and very elderly (≥ 85 years). No significant difference was observed in the contact rate for HF or COPD according to deprivation class.

Table 4.4 Contact rates for HF and COPD (per 100 population), stratified by year

Year	Patients with HF alone	Contact rate for HF (n)	Age standardised contact rate
1999	3712	82.5 (3061)	49.7
2000	4175	72.9 (3045)	38.8
2001	4373	57.0 (2494)	33.9
2002	4496	55.2 (2480)	39.2
2003	4451	50.8 (2262)	26.7
2004	4445	38.9 (1729)	23.5
			p for trend = 0.011
Year	Patients with COPD alone	Contact rate for COPD (n)	Age standardised contact rate
1999	7393	72.2 (5340)	44.6
2000	8369	67.4 (5640)	35.9
2001	8945	66.8 (5973)	40.7
2002	9520	65.6 (6241)	40.6
2003	9813	64.4 (6318)	42.8
2004	10242	60.9 (6241)	41.6
			p for trend = 0.85
Year	Patients with HF and COPD	Contact rate for HF or COPD (n)	Age standardised contact rate
1999	916	222.2 (2035)	130.1
2000	1078	202.5 (2183)	136.2
2001	1217	178.7 (2175)	135.0
2002	1333	168.4 (2245)	131.2
2003	1375	167.2 (2299)	137.7
2004	1389	135.8 (1886)	129.7
			p for trend = 0.96

4.3.5 Comorbidity in patients with HF with and without COPD

In 2003-4 the majority (76%) of patients with HF and COPD were recorded as current or previous smokers, as opposed to 47% of those without COPD ($p<0.001$). Despite this, the prevalence of smoking related cardiovascular and non-cardiovascular comorbidity was similar in the two groups (Table 4.5). This included prior history of myocardial infarction, angina, stroke and cancer. The prevalence of hypertension in HF patients with COPD was significantly lower than in those without COPD (49% vs 57%, $p<0.001$).

Table 4.5 Comorbidity in patients with HF, comparing those with and without COPD for April 2003 to March 2004

Condition n (%)	HF patients with COPD (n=1389)	HF patients without COPD (n=4445)	COPD patients without HF (n=10242)
Cardiovascular risk factors			
Diabetes	241 (17)	852 (19)	825 (8)
Hypertension	679 (49)*	2516 (57)	3446 (34)
Hypercholesterolaemia	288 (21)	923 (21)	1147 (11)
Smoker	660 (48)*	1171 (26)	5949 (58)
Ex-smoker	396 (29)*	931 (21)	2057 (20)
Cardiovascular disease			
Previous myocardial infarction	378 (27)	1264 (28)	660 (6)
Angina	737 (53)	2388 (54)	1882 (18)
Previous stroke	276 (20)	886 (20)	969 (10)
Atrial fibrillation	316 (23)†	1160 (26)	459 (5)
Non-cardiovascular comorbidity			
Cancer	381 (27)	1173 (26)	2398 (23)
Anxiety	359 (26)*	928 (21)	2640 (26)

*P<0.001 compared with patients without COPD, †P<0.05 compared with patients without COPD.

4.3.6 Pharmacological treatment of HF patients with and without COPD

Only 18% of patients with HF and COPD were prescribed β-blockers in 2003–4, as opposed to 41% of those without COPD (p<0.001). This contrasted strikingly with the prescription of ACE inhibitors, angiotensin receptor blockers, spironolactone and digoxin where no significant difference was noted between the groups (Table 4.6). More patients with COPD were prescribed loop diuretics (64% vs 55%, p<0.001) and calcium channel blockers (33% vs 27%, p<0.001). β-agonists were the most frequent therapy for COPD (57%), followed by inhaled corticosteroids (51%) and antimuscarinic drugs (24%). Despite having no formal diagnosis of COPD, 9% of the remaining patients with HF were prescribed β-agonists and 6% inhaled corticosteroids.

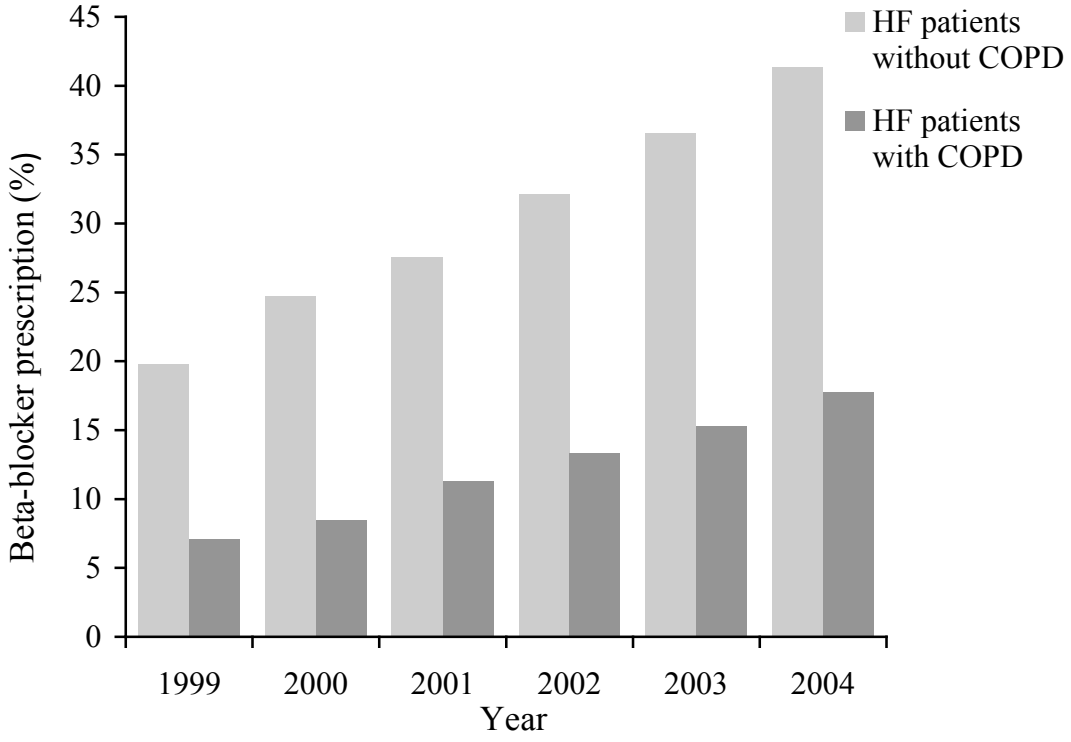
Table 4.6 Pharmacological treatment of patients with HF, comparing those with and without COPD for April 2003 to March 2004

Treatment n (%)	HF patients with COPD (n=1389)	HF patients without COPD (n=4445)	COPD patients without HF (n=10242)
Cardiovascular treatment			
β-blocker	246 (18)*	1838 (41)	1018 (10)
ACE inhibitor	671 (48)	2225 (50)	1625 (16)
Angiotensin receptor blocker	120 (9)	423 (10)	376 (4)
Spironolactone	151 (11)	406 (9)	85 (1)
Digoxin	230 (17)	784 (18)	183 (2)
Loop diuretic	893 (64)*	2462 (55)	1200 (12)
Calcium channel blocker	461 (33)*	1194 (27)	1933 (19)
Amiodarone	68 (5)	223 (5)	52 (1)
Aspirin	753 (54)	2524 (57)	2586 (28)
Clopidogrel	146 (11)†	380 (9)	365 (4)
Warfarin	219 (16)†	838 (19)	282 (3)
COPD treatment			
β-agonist	794 (57)*	395 (9)	5492 (54)
Inhaled antimuscarinic	333 (24)*	49 (1)	1750 (17)
Inhaled steroid	704 (51)*	255 (6)	4796 (47)
Oral steroid	300 (22)*	213 (5)	1873 (18)

*P<0.001 compared with patients without COPD, †P<0.05 compared with patients without COPD.

Overall prescribing of β-blockers in patients with HF increased from 17% to 36% between 1999 and 2004 (adjusted odds ratio 2.27 [95% CI 2.06–2.51], p<0.001). The proportion of patients being prescribed β-blockers increased from 20% to 41% in those without COPD, and from 7% to 18% in those with COPD (Figure 4.1). Patients with concurrent COPD were consistently less likely to receive β-blockers. There was no interaction between year of diagnosis and presence of COPD on the odds of being prescribed a β-blocker (p for interaction=0.848). The adjusted odds ratio for β-blocker prescription in those HF patients with COPD versus those without was 0.30 (95% CI 0.28–0.32).

Figure 4.1 Trends in β-blocker prescribing in patients with HF, comparing those with and without COPD



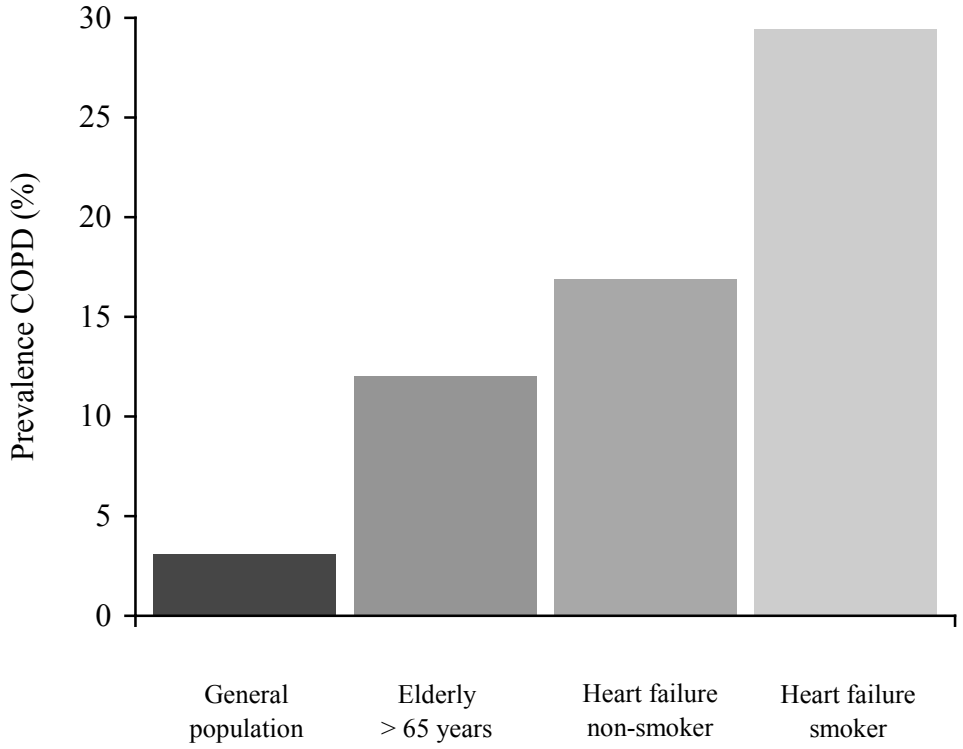
4.4 Discussion

This is the first study examining the epidemiology and management of patients with HF and coexistent COPD in the community.[1] Prior reports involved cohorts hospitalised with worsening HF,[97,167] attending specialised HF clinics,[171] or enrolled in clinical trials.[128,227] Using data collected in primary care I found that the prevalence of COPD in patients with HF increased year on year, was similar in men and women, and was associated with greater socioeconomic deprivation. Significantly, less than a fifth of patients with both HF and COPD in the community receive β-blockers and this has not improved over time.

4.4.1 Prevalence and incidence of COPD in patients with HF

Many factors influence estimates of COPD prevalence: surveillance systems, measurement techniques, diagnostic criteria applied, population age structure and risk factor exposure, most notably smoking.[59,309] The prevalence of COPD was approximately sevenfold greater in patients with HF than in the general primary care population. This predominantly reflects advancing age and smoking history (Figure 4.2).

Figure 4.2 Prevalence of COPD in selected populations for April 2003 to March 2004



The prevalence of COPD in the general practice population ≥ 65 years was 12%, closely matching that observed in the Cardiovascular Health Study (13%).[60] The reported prevalence of COPD in patients with HF ranges widely from 11% to

52% in North America, and from 9% to 41% in European cohorts.[1] The majority of studies were hospital rather than community based. However, the prevalence of 23.8% in 2004 is commensurate with a recent Dutch primary care study (24.5%).[69]

Between 1999 and 2004 the prevalence of COPD in patients with HF progressively increased from 19.8% to 23.8%. A similar trend was noted in three U.S. studies following patients hospitalised with HF during the 1990s.[63-65] These changes may previously have been attributed to an ageing population or increasing age of presentation.[1] However, the trend remained significant after age standardisation. The incidence of COPD in patients with HF has not previously been reported. As with prevalence, the age standardised rate increased significantly over time. These changes most likely reflect improved detection in primary care, although an increase in disease burden is also possible.

The prevalence and incidence of COPD were lowest in the young and very elderly under 55 and over 85 years of age respectively. This non-linear relationship between age and frequency of concurrent COPD has been noted previously.[66-69] It may be possible that the presence of COPD reduces survival beyond this age. Alternatively, the elderly may undergo less intensive diagnostic testing. Finally, a clear socioeconomic gradient was observed, with prevalence greatest in the most deprived. Smoking, the main risk factor for COPD, increased in parallel. Poor housing conditions, home dampness, urban habitats with greater air pollution and occupational differences may also contribute.[309,314]

4.4.2 Primary care burden

The impact of COPD on consultation rates in patients with HF has not previously been reported. As expected, the number of contacts for HF or COPD exceeded that for either condition alone. The trends in primary care burden proved more surprising. Both crude and age standardised contact rates for HF decreased by half between 1999 and 2004, whereas no significant change was observed in COPD consultation rates. These figures initially appear at odds with the aging population, declining mortality, and consequent increase in HF prevalence.[315] However, two crucial therapeutic interventions have accompanied these trends. B-blocker utilisation, which doubled during the same period, is associated with reduced hospitalisation rates.[316] A rapid expansion of nurse led intervention including home visits also occurred,[317] with proven reductions in emergency room and hospital attendances.[318] These improvements in clinical stability may well extend to primary care contact rates. In addition, the introduction of the Quality and Outcomes Framework (QOF) in the United Kingdom financially incentivised performance of echocardiography in patients with HF. Estimates of prevalence may decrease as incorrect diagnoses are removed from patients.

4.4.3 Comorbidity

A smoking history was present in 76% of patients with COPD, consistent with existing evidence.[309] A recent analysis of the Valsartan in Acute Myocardial Infarction trial reported clustering of cardiovascular risk factors (diabetes, hypertension, dyslipidaemia) and comorbidity (myocardial infarction, angina, stroke) in patients with COPD, associated with an increased risk of future atherosclerotic events.[227] That no such excess of smoking related cardiovascular disease was

observed is biologically implausible and cause for concern. A number of explanations are possible. Both patients and physicians may mistakenly attribute symptoms of angina or myocardial infarction to pulmonary disease. However, the diagnosis of hypertension or diabetes is based solely on objective measures. Airflow obstruction was associated with both these conditions in the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study.[243] The association between smoking and hypertension is equally well established.[319] This suggests that common cardiovascular risk factors are being under diagnosed (and likely under treated) in patients with HF and COPD.

4.4.4 Pharmacotherapy

Only one study from the UK DIN-LINK database has examined contemporary trends in β-blocker utilisation in primary care patients.[164] The overall prevalence of β-blocker prescription in 2005 (37%) was similar to the present study in 2004 (36%). As with previous reports,[164,168] I observed a steady rise in β-blocker use suggesting that evidence is translating into practice. Whether the gap between patients with and without COPD is diminishing was previously unknown. The results are disappointing. Despite the overall improvement, the relative difference between those with and without COPD remained unchanged. These findings are congruent with the Euro Heart Failure Survey, in which pulmonary disease was the most powerful independent predictor of β-blocker underutilisation (odds ratio 0.35 [0.30 - 0.40]).[173] Two simple facts should encourage improvement. Firstly, the majority of primary care patients with COPD have only mild or moderate airflow obstruction.[320] Secondly, the majority of patients with HF in the UK receive

bisoprolol which is highly cardioselective.[164,298] Only a small minority of patients will therefore be truly intolerant. With appropriate follow-up approximately 80% of patients with HF and COPD in the community tolerate β-blockade.[168,172]

Two other classes of medication are often overshadowed by the controversial issue of β-blockade and deserve mention. Patients with COPD were more frequently prescribed calcium channel blockers (33% vs 26%, $p<0.001$). Although dihydropyridine and non-dihydropyridine classes were not distinguished, rate limiting calcium channel blockers are often substituted for β-blockade in patients with coronary artery disease or arrhythmias. In patients with left ventricular systolic dysfunction these medications are associated with worsening heart failure and adverse cardiovascular events.[158,321] Inhaled β-agonists are likewise associated with increased hospitalisations and mortality in patients with LVSD.[249] β-agonists are first line therapy and a necessity in those with COPD. However, 9% of patients with HF but without COPD were also prescribed inhaled β-agonists. Although a small proportion may have asthma, physicians should be wary of prescribing bronchodilators to patients with HF before objectively demonstrating airflow obstruction.

4.4.5 Limitations

The limitations of epidemiological studies (such as unknown confounding) are well known. In addition, the evidence on which diagnoses are based was not recorded. Objective measures of HF and COPD severity are also unavailable. Patients with reduced and preserved left ventricular function are not differentiated: the evidence for prescribing β-blockers for HF with normal ejection fraction is

substantially weaker.[225] Nevertheless, the information provides a 'real world' perspective of patients with both conditions who are managed in primary care. Finally, changing incentives in primary care over time may influence reporting practices.[322]

4.5 Conclusion

The prevalence of COPD is increasing in patients with HF and creates major challenges in primary care. Consultation rates in patients with both conditions are higher than in patients with either condition alone. Each diagnosis requires objective testing to which access may be limited. This analysis suggests that COPD is a barrier to the diagnosis of cardiovascular comorbidity in patients with HF. The therapeutic consequences are equally concerning to primary care physicians. Underuse of β-blockers and inappropriate prescribing of β-agonists may both increase hospitalisations and mortality. In the Study of Heart Failure Awareness and Perception in Europe, COPD was a common perceived contraindication to β-blockade among primary care physicians.[310] In the United Kingdom, the Quality and Outcomes Framework financially remunerates practices achieving evidence based indicators. Remarkably, the heart failure QOF currently requires only that a patient undergoes echocardiography and receives treatment with either an ACE inhibitor or angiotensin receptor blocker.[323] The inclusion of β-blocker targets in the framework for 2009/10 will hopefully improve utilisation in those with concurrent COPD. Primary care physicians require greater support in managing patients with HF and COPD.

Chapter 5

How many patients with heart failure and chronic obstructive pulmonary disease receive or have alternative reasons precluding β-blockade?

5.1 Introduction

Chronic obstructive pulmonary disease is a frequent comorbidity in heart failure and a perceived contraindication to β-blockade. In the Euro Heart Failure Survey pulmonary disease was the most powerful independent predictor of β-blocker underutilisation (odds ratio 0.35 [95% CI 0.30 - 0.40]).[173] However, management of patients with both conditions poses complex patient level decisions which are inadequately assessed by epidemiological and cohort studies. Many simple clinical questions remain unanswered. How many patients have alternative reasons precluding β-blockade? How many have severe airflow obstruction? Do patients with COPD receive cardioselective β-blockers, and at what doses? How many HF patients without COPD receive inappropriate bronchodilator therapy? I performed a detailed case record review to define these issues.

5.2 Methods

5.2.1 Participants

Stobhill Hospital is a large urban hospital serving a local population of 200,000 people. Consecutive hospital admissions between June 2005 and March 2006 were included. Patients with heart failure were identified by an ICD 10 discharge code for HF in any diagnostic position. The following codes were used: 150.0, congestive heart failure 150.1, left ventricular failure; 150.9, heart failure unspecified; 111.0, hypertensive heart failure; 142.0, dilated cardiomyopathy; 125.5, ischaemic cardiomyopathy; 142.9, cardiomyopathy unspecified.

5.2.2 Data Retrieval

Stobhill Hospital employs an electronic 'incremental discharge letter system' for all hospital admissions. Two letters are produced for every patient. The first 'immediate' discharge summary is written by junior or middle grade doctors on the day of discharge. All medications are re-checked by the ward pharmacist. A subsequent 'final' discharge summary by middle grade or consultant physicians includes additional comments or corrections. The final discharge summaries and medications of all patients with HF were reviewed. I examined the case records of patients where a diagnosis of COPD was suggested by discharge code, physicians' comments, or prescription of inhalers. The results of investigations were retrieved from case records. Further data were acquired by searching databases of the radiology, echocardiography and pulmonary function departments. The use of anonymised data was discussed with the local ethics committee and did not require additional formal ethical approval.

5.2.3 Diagnostic Criteria

In accordance with European Society of Cardiology guidelines the diagnosis of HF required both compatible symptoms and objective evidence of cardiac dysfunction. Response to therapy was not mandatory but conferred added weight to the diagnosis of HF. The study aim was to examine patients with an indication for β-blocker treatment. Those with preserved systolic function were therefore excluded. Left ventricular systolic dysfunction was graded semi-quantitatively (mild, moderate or severely impaired) in accordance with the hospital's usual practice. Patients were

categorised according to physician diagnosis of COPD to reflect actual clinical practice. Severity of airflow obstruction was classified using the Global Initiative for Chronic Obstructive Lung Disease guidelines (Table 1.1).

5.2.4 Statistical Analysis

Baseline characteristics of patients with and without COPD are presented as means with standard deviations for continuous variables or by frequencies and percents for categorical variables. Means were compared using the Student t-test and proportions using the chi-square test. A 2-tailed P value of less than 0.05 was considered statistically significant.

5.3 Results

5.3.1 Prevalence of COPD

In total 449 consecutive HF admissions were screened for the presence of COPD. Miscoding, re-admissions, and patients with preserved systolic function were excluded (n=24, 108 and 55 respectively). Of the remaining admissions, 75 of 262 patients (29%) had a physician diagnosis of COPD. A smoking history was present in 83% of those with COPD. The demography, investigations and medications of patients with and without COPD are presented in Table 5.1. Both groups were elderly (mean age 76.2 ± 11.9 years) with similar proportions being male and female.

Table 5.1 Baseline characteristics of patients with heart failure according to COPD status

Characteristics	COPD n=75 (28.6%)	No COPD n=187 (70.4%)
Demographics		
Age (years)	75.7 ± 9.4	76.4 ± 12.7
Male	39 (52.0)	89 (47.6)
Cardiac Medications		
ACE inhibitor	36 (48.0)	109 (58.3)
Angiotensin receptor blocker	13 (17.3)	26 (13.9)
Spironolactone	13 (17.3)	28 (15.0)
Digoxin	25 (33.3)	42 (22.5)
Diltiazem	11 (14.7)*	5 (2.7)
β-Blocker	31 (41.3)	101 (54.0)
Loop Diuretic	68 (90.7)	163 (87.2)
Inhaled Therapy		
Short Acting β_2-Agonist	52 (69.3)*	4 (2.1)
Long Acting β_2-Agonist	39 (52.0)*	4 (2.1)
Inhaled Corticosteroid	52 (69.3)*	7 (3.7)
Tiotropium	24 (32.0)*	3 (1.6)
Nebulised β_2-Agonist	7 (9.3)*	1 (0.5)
Oral Corticosteroid	4 (5.3)†	1 (0.5)
Investigations		
Echocardiography Ever	70 (93.3)†	156 (83.4)
• LVSD Mild	18 (26.1)	38 (25.3)
• LVSD Moderate	32 (46.4)	56 (37.3)
• LVSD Severe	19 (27.5)	56 (37.3)
Chest Radiograph	75 (100.0)	184 (98.4)
• Cardiomegaly	50 (66.7)	137 (73.3)
• Pleural Effusions	29 (38.7)	84 (44.9)
• Alveolar Oedema	38 (50.7)	87 (46.5)
Pulmonary Function Tests	53 (70.7)*	35 (18.7)
• GOLD None	9 (12.0)	22 (11.8)
• GOLD Mild	14 (18.7)*	5 (2.7)
• GOLD Moderate	17 (22.7)*	7 (3.7)
• GOLD Severe	13 (17.3)*	1 (0.5)

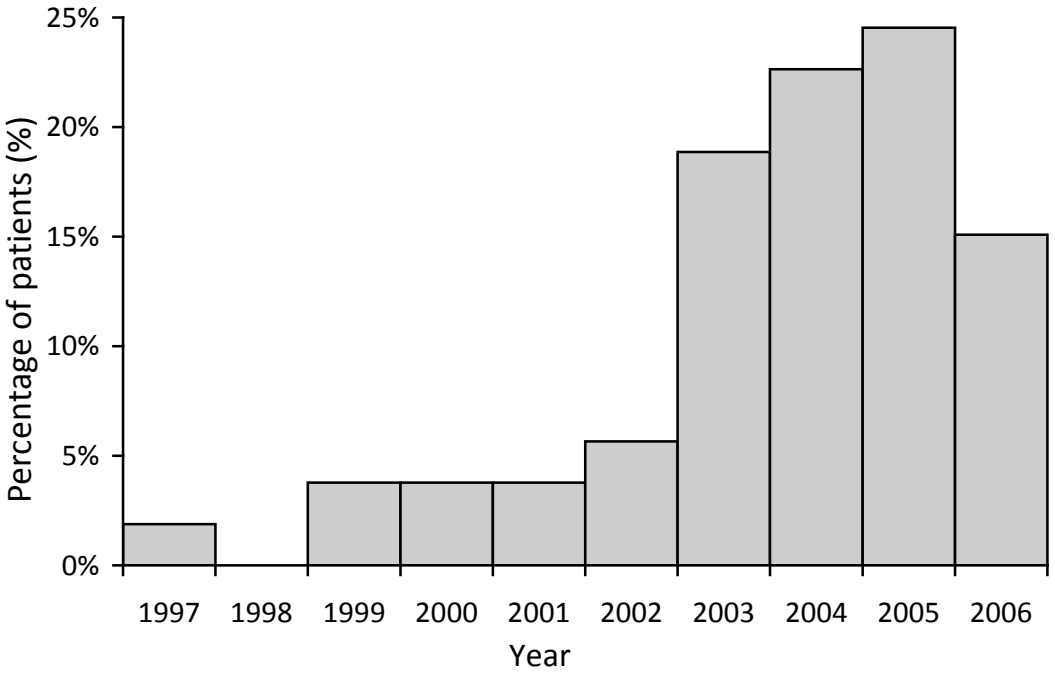
*P<0.001 compared with patients without COPD, †P<0.05 compared with patients without COPD. Values are means ± SD or n (%).

ACE, angiotensin converting enzyme; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LVSD, left ventricular systolic dysfunction

5.3.2 Investigations

Pulmonary function test results were available in 53 (71%) patients with COPD. Mean FEV_1 was 1.51L (± 0.58L) and mean percentage of predicted FEV_1 was 67% (± 20%). Only a minority had severe airflow obstruction (17%). Pulmonary function tests had been performed recently in many patients (Figure 5.1).

Figure 5.1 Date of pulmonary function testing in patients with heart failure and chronic obstructive pulmonary disease



Echocardiography results were available in 86% of patients with HF. No significant difference was observed in the severity of left ventricular systolic dysfunction between those with and without COPD. Radiological findings were likewise similar in the two groups.

5.3.3 Pharmacotherapy

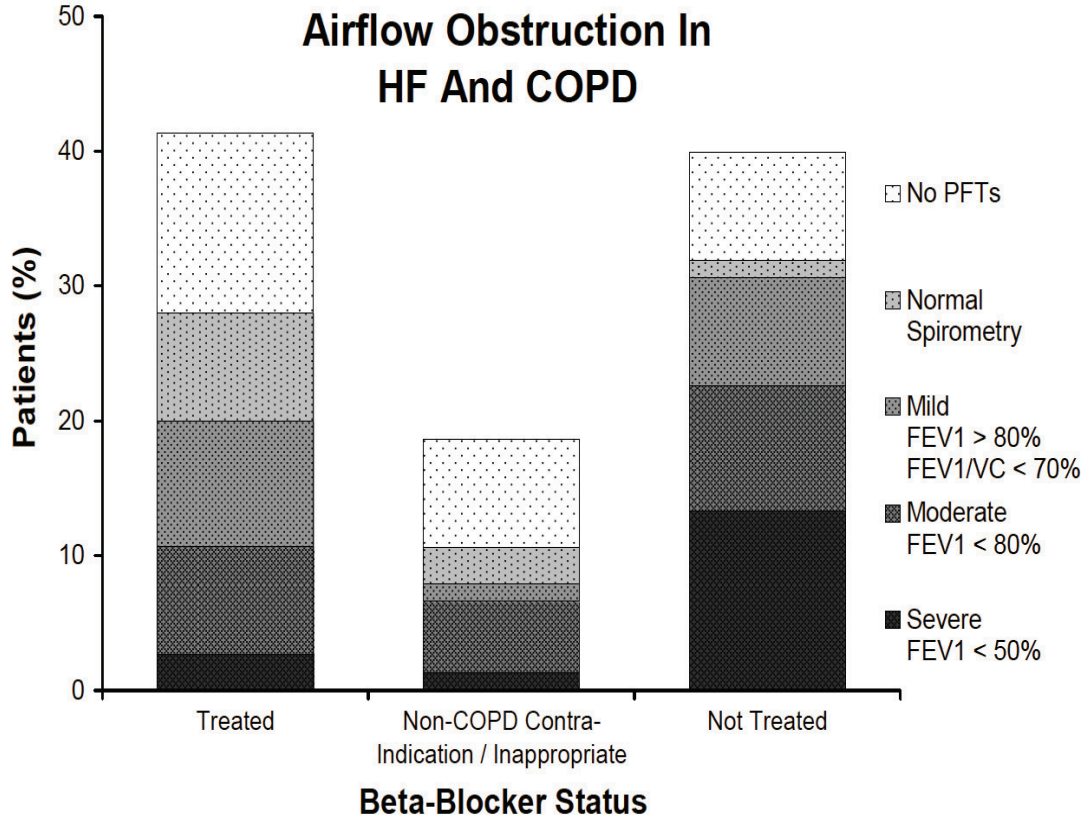
Patients with COPD were more often prescribed diltiazem compared to those without COPD (15% vs 3%, $p<0.001$). Short acting β-agonists and inhaled corticosteroids were the most frequent therapies for COPD (69%), followed by long acting β-agonists (52%) and antimuscarinic drugs (32%). Only a small proportion of

patients without a physician diagnosis of COPD received β-agonists (2%) or other bronchodilators.

5.3.4 β-blockade

31 (41%) of the 75 patients with COPD received β-blockers. In 19%, β-blockers were contraindicated or considered inappropriate for reasons other than COPD. These included bradycardia, conduction disturbance, hypotension, severe peripheral arterial disease or advanced malignancy and dementia. The remaining 30 patients (40%) did not receive β-blockers. 13% (n=10) had severe airflow obstruction (Figure 5.2).

Figure 5.2 β-blocker status and degree of airflow obstruction in patients with heart failure and chronic obstructive pulmonary disease



27% (n=20) had milder obstruction or no documented pulmonary function tests and may have been inappropriately denied treatment with a β-blocker. The choice and dose of β-blocker in patients with COPD was examined. Of the 31 patients, all but one received a cardioselective β-blocker. The mean dose expressed as a percentage of the maximum target dose was similar in those with and without COPD (37% vs 36% respectively).

5.4 Discussion

The present study addresses simple clinical issues that are overlooked by larger cohort studies or subgroup analysis of clinical trials. β-blocker utilisation is often criticised in patients with COPD. However, the proportion with alternative reasons precluding β-blockade was previously unclear. In approximately one fifth of patients, β-blockers were contraindicated or considered inappropriate for reasons other than COPD. Nevertheless, 27% of patients with HF and COPD failed to receive a β-blocker despite lacking severe airflow obstruction or an alternative reason precluding β-blockade.

Estimates of COPD prevalence vary according to the population studied, diagnostic criteria applied, measurement tools and surveillance systems.[59] The reported prevalence of COPD ranges from 11% to 52% in North American patients with HF, and from 9% to 41% in European cohorts.[1] The observed prevalence of 29% is consistent with contemporary European cohorts hospitalised with worsening HF.

Surprisingly few studies report the prevalence of β-blocker use in patients with HF and concomitant COPD (Table 1.6). Analysis from 152 UK general practices indicated that 24% of primary care patients with both conditions were prescribed β-blockers.[164] Italian and Danish studies observed comparable levels on admission to hospital with worsening HF in 241 and 182 patients with concurrent COPD (respectively 16% and 27%).[97,165] Similarly, 22% of patients with HF and COPD enrolled in the Valsartan Heart Failure Trial received β-blockers.[128] Four specialised HF clinics reported far higher but equally consistent results, with between 81% and 86% of outpatients with COPD tolerated β-blockers.[169-172]

The present cohort consisted of elderly hospitalised patients managed by general physicians and cardiologists. The prevalence of β-blockade in those with COPD (41%) was greater than observed in the community but lower than achieved in HF clinics. Numerous factors determine β-blocker utilisation: contraindications, including hypotension, bradycardia, high grade atrioventricular block, severe peripheral arterial disease or airflow obstruction;[168,169,324-326] ineligibility due to advanced malignancy, dementia or general frailty;[325] and symptomatic intolerance or patient choice.[168,169,172,325,326] Referral bias undoubtedly excludes many ineligible patients from HF clinics. The prevalence of β-blocker use is consequently lower in unselected populations. However, one factor remains a barrier to β-blocker therapy irrespective of patient characteristics or the clinical setting: physicians' perception. In the recent Study of Heart Failure Awareness and Perception in Europe,[310] COPD was a common perceived contraindication to β-blockade among general internists and primary care physicians.

β-blockade was cardioselective in almost all patients, with no dose reduction associated with the presence of COPD. The explanation is twofold. Firstly, the majority of patients with HF in the UK receive bisoprolol.[164] Secondly, cardioselective β-blockers are well tolerated in patients with mild to moderate COPD.[2] Only one other report has assessed β-blocker dose in patients with HF and COPD, likewise finding no difference between those with and without airflow obstruction.[172]

A recent US study revealed significant disparities in confirmatory testing practices.[58] Among 219 patients discharged from a tertiary centre with both HF and COPD, 82% had documented echocardiography as opposed to 36% pulmonary function testing. I found less discrepancy between investigations. The majority of patients had spirometry results available, most performed in recent years. This is reassuring, as both inhaled therapy and β-blockade are dictated by the degree of airflow obstruction. Only one previous study has defined the severity of airflow obstruction in patients with HF and COPD according to GOLD criteria.[171] Severe obstruction was found in 23% of the 73 patients, akin to the 17% observed in my cohort.

Two other classes of medication are often overshadowed by the controversial issue of β-blockade and merit consideration. Patients with COPD were more frequently prescribed diltiazem (15% vs 3%, $p<0.001$). Rate limiting calcium channel blockers are often substituted for β-blockade in patients with coronary artery disease or arrhythmias. In patients with LVSD these medications are associated with worsening heart failure and adverse cardiovascular events.[158,321,327] Extensive safety data from the BEAUTIFUL trial now supports the use of ivabradine in patients with

LVSD and coronary artery disease.[328] This should provide a safer alternative to diltiazem in patients with HF and COPD who are truly intolerant of β-blockade. Finally, inhaled β-agonists are associated with increased hospitalisations and mortality in patients with LVSD.[249] β-agonists are first line therapy and a necessity in those with COPD. However, they represent an unnecessary risk and should be avoided in the absence of COPD. I observed a low prevalence of bronchodilator use in such patients.

Several limitations to the present study must be acknowledged, foremost being the retrospective data collection. Data loss was minimised by searching multiple electronic databases in addition to the printed case records. Reasons for β-blocker intolerance may not always be documented. I examined only discharge medications as this information was checked by both doctors and pharmacists. Comparing these to admission medications may have provided useful information regarding discontinuation of therapy.

5.5 Conclusion

Patients with HF and COPD often tolerate or have alternative reasons precluding β-blockade. Only a minority have severe airflow obstruction. The remainder may have β-blocker therapy inappropriately withheld. I estimate an achievable target for β-blocker utilisation lies between 60% and 70% in unselected patients with HF and COPD. Regional or national registries (such as ADHERE or OPTIMIZE-HF)[329,330] are needed for prospective data collection and quality improvement. Using pre-discharge protocols improves the prescription of β-

blockers.[331] These measures would promote higher levels of β-blocker use and help inform clinical practice.

Chapter 6

Chronic obstructive pulmonary disease is an independent predictor of death but not atherosclerotic events in patients with myocardial infarction: analysis of the Valsartan in Acute Myocardial Infarction trial (VALIANT).

6.1 Introduction

Chronic obstructive pulmonary disease is a global epidemic affecting 5 to 15% of all adults.[309] Both prevalence and mortality are increasing and projected to escalate still further. Cardiovascular and pulmonary deaths are equally common, accounting for 3 million lives per year worldwide.[332] The shared aetiology of tobacco smoking is partly responsible. However, airflow obstruction independently predicts cardiovascular mortality in population studies, even after adjusting for smoking history.[143] Atherosclerotic consequences of chronic systemic inflammation in COPD have been postulated.[139,333,334] Whether these aggravate established coronary artery disease is uncertain.

Two contemporary studies have examined patients with myocardial infarction and concomitant COPD.[335,336] Both found COPD to be an independent predictor of long term mortality.[335,336] Neither report investigated the relationship between COPD and mode of death or risk of non-fatal cardiovascular events. Furthermore, the increased mortality was confined to patients without heart failure (HF) in one study.[335] I used the Valsartan in Acute Myocardial Infarction (VALIANT) trial to characterise the impact of COPD on treatment and clinical outcomes in patients with MI complicated by heart failure, left ventricular systolic dysfunction, or both.

6.2 Methods

6.2.1 Trial design

VALIANT enrolled 14,703 patients with myocardial infarction complicated by left ventricular systolic dysfunction, heart failure, or both. The former was defined by ejection fraction≤ 0.35 on echocardiography or contrast angiography and ≤ 0.40 on radionuclide ventriculography, the latter by clinical signs of heart failure or radiologic evidence of pulmonary venous congestion.[337] The randomised, double-blind, active-controlled design compared treatment with valsartan, captopril, or both. The rationale, methods, inclusion and exclusion criteria and main outcomes have been reported previously.[337,338] The study was approved by local ethics committees in all participating centres and all patients provided written informed consent.

6.2.2 Trial endpoints

The primary outcome was mortality from any cause within 3 years following the index MI. Secondary prespecified endpoints included: cardiovascular death and components (sudden cardiac death, fatal myocardial infarction and fatal worsening HF); non-fatal myocardial infarction; hospital admission for worsening HF; and the composite of cardiovascular death, myocardial infarction, or HF hospitalisation. Presence of clinically recognised COPD was recorded using a yes/no check box by individual site investigators at study entry according to their clinical judgement.

All prespecified endpoints were adjudicated by an independent clinical endpoint committee. Definitions of the endpoints are published previously.[338] Hospitalisation for HF was defined as admission with symptoms or signs of HF requiring intravenous treatment with diuretic, inotropic, or vasodilator therapy. Members of the committee distinguished HF from COPD using clinical judgement supported by hospital records and results of investigations.

6.2.3 Statistical analysis

Data analyses were performed independently by the Duke Clinical Research Institute. The COPD status is defined as having a known history prior to the qualifying MI for the trial. Baseline characteristics of patients with and without COPD are presented as means with standard deviations for continuous variables or by frequencies and percents for categorical variables. Means were compared using the Wilcoxon rank sum test or Student t-test depending on the distribution of the data, and proportions using the Chi-square test. All analyses were performed on an intention to treat basis. Cumulative event rates were estimated using the Kaplan-Meier method and were compared using log-rank test. A 2-tailed P value of less than 0.05 was considered statistically significant.

The prognostic significance of COPD was evaluated for predefined outcomes, including the primary endpoint and other major cardiovascular events. The estimated hazard ratios were adjusted for all important predictors of mortality and morbidity using Cox proportional hazards models. A separate model was built for each outcome of interest. Starting from over 70 candidate variables collected at randomisation, both backward elimination and stepwise selection were used to identify independent factors. A p value of 0.10 was required for a variable to enter and 0.05 to stay in the model. Bootstrap method with a resample of 200 was employed to validate the selection. Randomised treatments were added to the final model. The multivariable model for mortality included the following covariates: age, heart rate, systolic and diastolic blood pressure, weight, baseline creatinine, smoking status, diabetes, dyslipidaemia, history of hypertension, Killip classification, anterior

MI, new left bundle branch block, thrombolytic therapy, primary percutaneous intervention, coronary artery bypass graft surgery after the qualifying MI, history of heart failure, atrial fibrillation, previous MI, angina or unstable angina, previous stroke, peripheral arterial disease, renal insufficiency, alcohol abuse, country of enrolment, β-blocker use, randomised treatment. The multivariate model for mortality stratified by COPD status and baseline β-blocker was employed to estimate the adjusted death rates for each of the four strata at different time points within the 3 year follow-up period. Event curves were created to display the cumulative adjusted mortality rates over time (Figure 6.1).

An analysis of post randomisation periods ('landmarks') was employed to address potential survivor bias in analysis of the composite atherosclerotic outcome of MI or stroke. Patients with COPD may die earlier than their counterparts, before developing arterial disease. The association between COPD and atherosclerotic events may thus be underestimated due to unequal survivorship. To minimise this effect, the relationship between COPD and atherosclerotic events was examined in four different periods: inpatient (1–16 days since randomisation), post discharge (17–45 days), early (46–198 days) and later (199–1096 days) follow-up. Only patients alive at the beginning of each period were included in each analysis. When the risk is similar cross intervals, a combined HR was estimated by treating each interval as a cluster in the Cox model. All analyses were performed using SAS software version 8 (SAS Institute, Cary, North Carolina).

6.3 Results

6.3.1 Baseline Characteristics

VALIANT enrolled 14703 patients, 1258 (8.6%) of which had a diagnosis of COPD. The median duration of follow-up was 24.7 months. The baseline characteristics of patients with and without COPD differed significantly (Table 6.1).

Table 6.1 Baseline characteristics of patients with COPD

Characteristics	COPD Beta-Blocker n=643 (4.4%)	COPD No Beta-Blocker n= 615(4.2%)	No COPD Beta-Blocker n=9709 (66.0%)	No COPD No Beta-Blocker n=3736 (25.4%)
Demographics				
Age (years) *	67.0 ± 10.1	69.2 ± 9.5	63.5 ± 12.1	67.3 ± 11.1
Female Sex	166 (25.8)	197 (32.0)	2915 (30.0)	1291 (34.6)
Body Mass Index (kg/m^2)†	28.1 ± 5.6	26.9 ± 5.4	28.0 ± 4.8	27.6 ± 4.9
CV Risk Factors				
Current smoker*	277 (43.1)	251 (40.8)	3114 (32.1)	1022 (27.4)
Previous smoker*	259 (40.3)	259 (42.1)	2966 (30.6)	1195 (32.0)
Diabetes mellitus†	178 (27.7)	145 (23.6)	2047 (21.1)	1029 (27.5)
Hypertension†	397 (61.7)	334 (54.3)	5326 (54.9)	2063 (55.2)
Dyslipidaemia*	257 (40.2)	196 (32.4)	2883 (30.2)	998 (27.2)
Previous Comorbidity				
Heart failure*	163 (25.3)	180 (29.3)	1184 (12.2)	647 (17.3)
Myocardial infarction*	274 (42.6)	228 (37.1)	2512 (25.9)	1090 (29.2)
Angina*	297 (46.2)	283 (46.0)	3680 (37.9)	1581 (42.3)
PCI*	88 (13.7)	50 (8.1)	724 (7.5)	205 (5.5)
Stroke†	53 (8.2)	50 (8.1)	545 (5.6)	247 (6.6)
Peripheral arterial disease*	119 (18.5)	101 (16.4)	670 (6.9)	347 (9.3)
Atrial fibrillation*	47 (7.3)	73 (11.9)	533(5.5)	307 (8.2)
Characteristics of MI				
Heart Rate*	75.5 ± 12.7	81.1 ± 13.7	74.6 ± 12.3	79.6 ± 13.2
Systolic BP (mm Hg)†	123.1 ± 16.3	124.7 ± 17.4	122.0 ± 16.7	123.9 ± 17.6
Diastolic BP (mm Hg)†	71.0 ± 11.4	71.6 ± 11.2	72.2 ± 11.2	73.1 ± 11.5
Killip class III-IV*	148 (23.0)	221 (35.9)	1847 (19.0)	1244 (33.3)
Radiologic LV failure†	251 (39.0)	283 (46.0)	3412 (35.1)	1796 (48.1)
ECG Site – Anterior*	324 (53.7)	283 (48.9)	5768 (61.8)	2016 (56.1)
Q-wave MI*	324 (53.3)	308 (52.9)	6413 (68.4)	2396 (66.4)
Non Q-wave MI*	267 (44.6)	253 (44.0)	2812 (30.4)	1126 (31.7)
Ejection fraction	34.2 (9.9)	33.8 (10.4)	35.5 (10.2)	35.1 (10.8)
Initial Treatment of MI				
Aspirin*	547 (85.1)	518 (84.2)	8783 (90.5)	3233(86.5)
Thrombolysis*	178 (27.7)	168 (27.3)	3733 (38.5)	1090 (29.2)
Catheterisation	205 (31.9)	147 (24.0)	2959 (30.5)	810 (21.7)
Primary PCI*	72 (11.2)	61 (9.9)	1646 (17.0)	398 (10.6)
Medications				
Aspirin*	572 (89.0)	529 (86.0)	9044 (93.2)	3273 (87.6)
β-blocker*	643 (51.1)	0 (0)	9707 (72.2)	0 (0)
Digoxin*	125 (19.4)	143 (23.3)	941 (9.7)	647 (17.3)
Statin	244 (37.9)	155 (25.2)	3702 (38.1)	913 (24.4)
Calcium channel blocker*	76 (11.8)	138 (22.4)	619 (6.4)	428 (11.5)

*P<0.0001 compared with patients without COPD, †P<0.05 compared with patients without COPD.

Values are means ± SD or n (%).

COPD = chronic obstructive pulmonary disease; CV = cardiovascular; ECG = electrocardiogram; PCI = percutaneous coronary intervention; MI = myocardial infarction.

Patients with COPD were older with more cardiovascular risk factors including current or previous smoking, diabetes, hypertension and dyslipidaemia. Comorbidity was likewise greater in patients with COPD, particularly coronary (MI, PCI, angina), peripheral and cerebrovascular disease. At randomisation patients with COPD had a higher heart rate, Killip classification and frequency of radiological pulmonary oedema. The qualifying electrocardiogram and ensuing treatment also varied. Patients with COPD more frequently presented with non Q-wave MI (44.3% vs 30.8%). Fewer patients with COPD received primary percutaneous intervention (10.6% vs 15.2%) or thrombolysis (27.5% vs 35.9%), although a similar proportion underwent cardiac catheterisation. Patients with COPD were less likely to receive some risk-modifying cardiovascular medications, most notably β-blockers (51.1% vs 72.2% at randomisation).

6.3.2 Mortality

COPD was independently associated with increased mortality. A total of 382 patients with COPD (30.4%) died from any cause, compared with 2496 (18.6%) of those without (Table 6.2). After adjusting for additional predictors of mortality, the risk of death was increased by 14% in patients with COPD (HR 1.14 [95% CI 1.02–1.28]). Mortality was greater in those with COPD, regardless of β-blocker prescription (Figure 6.1). Increased incidence of both non-cardiovascular death (6.0% vs 2.4%, HR 1.86 [1.43–2.42]) and sudden death (10.0% vs 5.9%, HR 1.26 [1.03–1.53]) contributed to the excess mortality in patients with COPD (Table 6.2).

However, the overall risk of cardiovascular death was not significantly elevated after correcting for baseline differences. The increased risk of sudden death was independent of age, β-blocker use, ischaemic heart disease, diabetes and other recognised predictors of sudden death. Of the 75 non-cardiovascular deaths in patients with COPD, two thirds were attributed to pulmonary disease (25%, n=19), malignancy (33%, n=25) or infection (9%, n=7). The respective frequencies in patients without COPD were 9% (n=30), 43% (n=137) and 13% (n=43).

Table 6.2 Risk of death and cardiovascular events in patients with COPD

Outcome	COPD present n=1258 (%)	COPD absent n=13445 (%)	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
All cause mortality	382 (30.4)	2496 (18.6)	1.70 (1.53-1.90)	<0.0001	1.14 (1.02-1.28)	0.021
Non-cardiovascular death	75 (6.0)	319 (2.4)	2.61 (2.02-3.36)	<0.0001	1.86 (1.43-2.42)	<0.0001
Cardiovascular death	307 (24.4)	2177 (16.2)	1.57 (1.39-1.77)	<0.0001	1.04 (0.92-1.19)	0.506
Sudden death	126 (10.0)	799 (5.9)	1.77 (1.47-2.14)	<0.0001	1.26 (1.03-1.53)	0.025
HF hospitalisation	317 (25.2)	2071 (15.4)	1.77 (1.57-1.99)	<0.0001	1.19 (1.05-1.34)	0.007
MI or stroke	190 (15.1)	1570 (11.7)	1.58 (1.27-1.94)	<0.0001	0.98 (0.77-1.23)	0.871
CV death, MI, HF hospitalisation	567 (45.1)	4047 (30.1)	1.64 (1.50-1.79)	<0.0001	1.14 (1.04-1.25)	0.005

COPD = chronic obstructive pulmonary disease; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MI = myocardial infarction.

6.3.3 Cardiovascular Morbidity and Mortality

COPD was an independent predictor of hospitalisation for heart failure (HR 1.19 (1.05–1.34). The combined endpoint of CV death, MI or HF hospitalisation occurred in 45% of patients with COPD, compared to 30% of those without. The

adjusted risk for the combined endpoint remained significantly increased in patients with COPD (1.14 [1.04-1.25]).

A composite atherosclerotic outcome was examined, incorporating fatal or non-fatal MI and stroke. This combined endpoint occurred in 190 (15.1%) as opposed to 1570 (11.7%) patients with and without COPD respectively. The adjusted risk of atherosclerotic events was not increased (0.98 [0.77–1.23], p=0.871). According to the analysis of landmarks, the adjusted HR of the relation between COPD and atherosclerotic events was 0.94 ([0.70–1.25], p=0.657), 1.36 ([0.96–1.93], p=0.085), 0.91 ([0.71–1.17], p=0.381) and 0.86 ([0.70–1.07], p=0.648) for inpatient, post discharge, early and later follow up respectively. The higher hazard of atherosclerotic events during the post discharge period was not statistically significant (p=0.085). Combining results from all periods yielded a similar hazard ratio (0.94 [0.81–1.08], p=0.348).

The impact of COPD on atherosclerotic events was far outweighed by alternative cardiovascular risk factors (Table 6.3). The chi square statistic indicates the relative contribution of each factor to the variance of the outcome. Multivariate analysis revealed diabetes to be the strongest determinant of MI or stroke (HR 1.36 [1.24–1.50] , p<0.001). Smoking, hypertension, obesity and established coronary, peripheral and cerebrovascular disease were all independent predictors of atherosclerotic events.

Table 6.3 Independent predictors of myocardial infarction or stroke

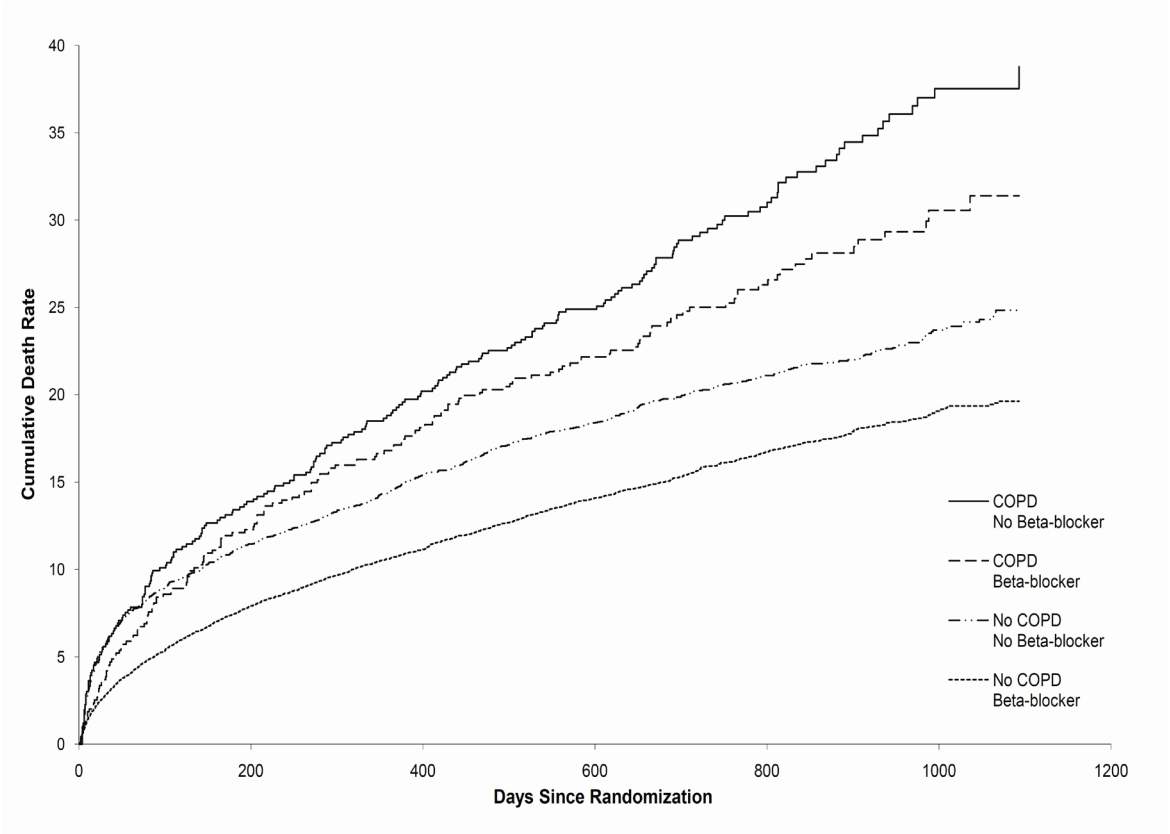
Predictor	Hazard Ratio (95% CI)	p value
Diabetes	1.36 (1.24-1.50)	<0.001
Age (per 10 years)	1.17 (1.11-1.24)	<0.001
Angina	1.31 (1.19-1.44)	<0.001
Previous MI	1.28 (1.16-1.42)	<0.001
Killip Class 3	1.42 (1.22-1.66)	<0.001
Killip Class 4	1.49 (1.23-1.81)	<0.001
Previous stroke	1.28 (1.12-1.47)	<0.001
Heart failure post-MI	1.19 (1.08-1.31)	<0.001
Heart rate (per 10 bpm)	1.06 (1.03-1.10)	<0.001
Current smoker	1.21 (1.08-1.36)	0.002
Previous unstable angina	1.17 (1.06-1.30)	0.002
Hypertension	1.17 (1.06-1.30)	0.002
Angina post-MI	1.16 (1.05-1.28)	0.003
Peripheral vascular disease	1.19 (1.05-1.35)	0.007
Killip Class 2	1.18 (1.03-1.34)	0.014
New diabetes	1.28 (1.04-1.57)	0.018
Left bundle branch block	1.23 (1.03-1.45)	0.019
Weight (per 10 kg)	1.55 (1.07-2.22)	0.019
Previous CABG	1.19 (1.03-1.37)	0.020
Previous heart failure	1.13 (1.01-1.26)	0.035

CABG = coronary artery bypass grafting; CI = confidence interval; MI = myocardial infarction.

6.3.4 Relationship Between β-Blocker Use And Outcomes

Mortality was significantly lower in patients receiving β-blockers, irrespective of airways disease (Figure 6.1). Overall, the adjusted hazard ratio for mortality comparing patients with and without β-blockade was 0.74 [0.68–0.80], p=0.002. In patients with COPD, 25.2% of those prescribed β-blockers died from any cause, compared to 35.0% of those not prescribed β-blockers. Results were similar in patients without COPD (mortality 15.1% vs 27.9% respectively). Formal testing for interaction between COPD and β-blocker use with respect to mortality revealed no significant difference. β-blocker use was not associated adversely with any pre-specified outcome in patients with COPD.

Figure 6.1 Adjusted cumulative all cause mortality rate by COPD status and β-blocker use



6.4 Discussion

Numerous studies have addressed the prognosis of patients with myocardial infarction, heart failure, or both. Remarkably few have described the impact of pulmonary comorbidity. COPD is known to independently reduce survival after myocardial infarction.[335,336] My findings extend prior reports by defining the relative risk of cardiovascular and non-cardiovascular death, together with ischaemic and non-fatal events.

COPD was an independent predictor of mortality, largely due to increased non-cardiovascular and sudden death. The former is expected. Cigarette smoking

and COPD predispose to fatal outcomes from malignancy, pneumonia and respiratory failure.[339] The excess risk of sudden death corroborates findings of the recent TORCH (Towards a Revolution in COPD Health) trial.[291] This was the first international trial of COPD therapy to employ all cause mortality as the primary endpoint, and the first to adjudicate cause of death using a clinical endpoint committee. 16% of deaths were classified as sudden, and speculated to be the consequence of acute respiratory failure.[339]

Sudden death was explicitly defined in VALIANT as death that occurred suddenly and unexpectedly in a patient in otherwise stable condition and included witnessed deaths.[340] Some out of hospital acute respiratory failure may be included in the category of sudden death. However, numerous substrates for ventricular arrhythmia exist in patients with COPD: hypoxia, acidosis, hypercapnia, sympathetic activation, tachycardia, hypokalaemia and QTc prolongation secondary to inhaled β_2-agonists.[234,235] Although safe in unselected populations, inhaled β_2-agonists may precipitate cardiovascular events in susceptible patients.[234,235,249] After myocardial infarction the risk of sudden death is greatest in the early months and among those with lowest ejection fraction.[340] In high risk patients with COPD, early treatment of exacerbations and correction of arrhythmic substrates is therefore paramount.

In a recent cohort study of 2481 patients presenting with acute MI, rehospitalisation rates were 22% higher among patients with COPD.[336] The reasons for admission were not defined. The present analysis reveals COPD to be an independent predictor of HF hospitalisation after infarction. This mirrors findings in patients with chronic HF, in whom COPD is a frequent comorbidity and infection a recognised precipitant of decompensation.[78,86] Once hospitalised, concomitant

pulmonary disease also prolongs inpatient stay and increases risk of readmission.[78,103]

COPD is increasingly considered a systemic inflammatory disorder with putative atherosclerotic consequences.[139,333,334] The hypothesis is founded on the epidemiological association between airflow obstruction and cardiovascular mortality.[143] The key issue is whether COPD contributes to atherosclerosis, or merely serves as a marker of cardiovascular disease. This is the first analysis to evaluate COPD as a modifier of cardiovascular events in subjects with pre-existing coronary disease. Previous studies have focused on overall survival following myocardial infarction,[228,335,336,341] percutaneous intervention,[342,343] or surgical revascularisation.[344,345] Although I expected a strong association with atherosclerotic events, this was not found and merits careful consideration.

Many population studies adjusted only for age, gender and smoking history.[143] Residual confounding by established risk factors and unmeasured variables limits such reports. Numerous potential confounders exist: diabetes, hypertension, blood pressure, dyslipidaemia, low socioeconomic class, occupation, poor diet, sedentary lifestyle and obesity. In the high risk VALIANT cohort, all major cardiovascular risk factors occurred more frequently among patients with COPD. The prevalence of existing coronary, peripheral and cerebrovascular disease was likewise increased. Finally, patients with COPD received fewer risk-modifying medications, notably β-blockers. All these factors are established predictors of worse clinical outcomes. Comprehensive multivariate adjustment is thus crucial when considering prognosis. The 58% increased risk of atherosclerotic events was reduced by adjusting in multivariate analyses (HR 0.98 [0.77-1.23]). Exploring the relative

contribution of covariates to the atherosclerotic endpoint confirmed my suspicions. The independent predictors of MI or stroke were all established cardiovascular risk factors or comorbidity. These findings corroborate those of the TORCH study, in which just 3% of the 911 adjudicated deaths were attributed to myocardial infarction.[339]

Population studies have further limitations. Survival estimates are potentially biased by loss to follow-up. Reliance on hospital coding and death certificates overestimates the burden of cardiovascular events in the community.[346,347] Sudden death may be incorrectly attributed to coronary events. As discussed earlier, there are numerous other arrhythmic substrates.[234,235] Unmeasured changes in baseline risk factors may influence survival during long follow-up periods. Differences in cardiovascular treatment are likewise unaccounted for. β-blockers are underutilised in patients with airflow obstruction and concomitant hypertension, heart failure, angina or myocardial infarction.[173,229] The robust epidemiological association between airflow obstruction and cardiovascular mortality does not necessarily equate to COPD causing atherosclerosis.

Two observational cohort studies from the Cooperative Cardiovascular Project suggested β-blockers are safe and effective post MI in patients with COPD.[228,229] Neither reported the outcomes of patients with HF or LVSD. The present analysis extends the prognostic benefit of β-blockade to this important patient group. Furthermore, no adverse effects were observed for any prespecified endpoint. In particular, non-cardiovascular mortality was not increased in patients with COPD receiving β-blockers. This observation should help alleviate historical concerns regarding safety. As with previous reports,[228,229] interpretation is hindered by the

lack of spirometry or stratification of COPD severity. Recruitment bias and preferential prescribing habits confound applicability to patients with severe or reversible airflow obstruction.

Several limitations must be acknowledged, foremost being the investigator derived diagnosis of COPD. This was obtained from hospital records, pulmonary function if available, and questioning the patient. No prespecified criteria were defined in the investigators brochure. Misdiagnosis is unavoidable and inherent to all clinical trials lacking spirometry.[128,335,341] The prevalence of COPD in VALIANT (8.6%) was akin to these trials and also the general population.[128,335,341,348] No study has assessed the validity of self-reported COPD in patients with myocardial infarction. Only one has examined those admitted with heart failure, confirming airflow obstruction in 67%.[165] However, the proportion of that cohort with HF and COPD was higher than in VALIANT (HF 100% vs 15% and COPD 22% vs 9%), providing far greater scope for misdiagnosis. Furthermore, the VALIANT COPD group is characterised by the three major predictors of COPD: male gender (71%), advanced age, and smoking history (83%).[349,350] Recruitment bias will exclude many individuals with severe pulmonary disease. However, the generalisability of results is reasonable as severe airflow obstruction is also uncommon in the wider population.[139]

6.5 Conclusion

In summary, COPD is an independent predictor of mortality in patients with myocardial infarction, specifically of non-cardiovascular and sudden death. No

excess risk of atherosclerotic events was observed after adjusting for baseline risk factors and comorbidity. The proposed atherosclerotic effects of COPD are of limited clinical significance, at least during intermediate follow-up. There is a simple message. We must optimise both pulmonary and cardiovascular therapies in patients with COPD. Greater collaboration is required between the specialties to achieve this. Intensive treatment of established cardiovascular risk factors and disease is essential to improve outcomes in this high risk group.

Chapter 7

Baseline characteristics and outcomes of patients with heart failure receiving bronchodilators: evidence from the CHARM programme.

7.1 Introduction

Heart failure and chronic obstructive pulmonary disease are common partners with common problems.[1] Remarkably few studies have addressed this intersection between cardiovascular and pulmonary disease. The combination presents diagnostic challenges,[1] limits the use of β-blockers,[173] and is associated with worse survival.[1] The causes of higher mortality have been studied in a very limited fashion.[128] Use of bronchodilators, both β-agonist and antimuscarinic, is associated with adverse cardiovascular outcomes in patients with pulmonary disease.[234,235,247,251,351] The prognosis of patients with HF prescribed bronchodilators is however ill defined.[248,249] In particular there is little information regarding the prevalence of bronchodilator use in HF with and without systolic dysfunction, or the relationship between bronchodilator use and outcomes. In the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) programme, candesartan significantly reduced cardiovascular deaths and hospital admissions for heart failure.[352] The CHARM programme provides a unique opportunity to examine the prevalence and prognostic implications of bronchodilator use in a large cohort of patients with HF and wide range of left ventricular ejection fraction.

7.2 Methods

7.2.1 Trial design

Patients with symptomatic heart failure (New York Heart Association class II-IV) receiving standard therapy were enrolled into one of three parallel clinical

trials according to LVEF and angiotensin converting enzyme inhibitor treatment: LVEF ≤ 40% and not receiving an ACEI due to previous intolerance (CHARM-Alternative); LVEF ≤ 40% receiving ACEI treatment (CHARM-Added); and LVEF > 40% (CHARM-Preserved). There were 7599 patients randomised, 3803 receiving candesartan and 3796 placebo: 2028 in CHARM-Alternative, 2548 in CHARM-Added, and 3023 in CHARM-Preserved. Details of the rationale, methods, exclusion criteria and main outcomes have been published previously.[352-354] The study was approved by local ethics committees in all participating centres and all patients provided written informed consent.

7.2.2 Trial endpoints

The primary outcome was a composite of cardiovascular death or unplanned hospital admission for management of worsening HF. Secondary pre-specified endpoints and components included: cardiovascular death; hospital admission for HF; and composite of cardiovascular death, hospital admission for HF, non-fatal myocardial infarction or non-fatal stroke. The present study focused on the associations between bronchodilators and cardiovascular events in the cohorts with reduced (combined CHARM-Alternative / Added) and preserved (CHARM-Preserved) LV systolic function. Investigators at each participating centre employed a checkbox to record the use of bronchodilator therapy at baseline. The specific type of bronchodilator was not recorded.

7.2.3 Statistical analysis.

All data analyses were performed independently by the Medical Statistical Unit at the London School of Hygiene and Tropical Medicine, London, UK. Baseline characteristics of patients prescribed bronchodilators were summarised by mean (standard deviation) for continuous variables and by frequency (percentages) for categorical variables. Means were compared using the Student t-test and proportions compared using the chi-square test. All analyses were performed by intention to treat. The prognostic significance of bronchodilator use was evaluated for predefined clinically relevant outcomes, including the primary outcome and other major cardiovascular events.

The estimated hazard ratios were adjusted for all important predictors of mortality and morbidity identified in the CHARM programme,[355] including age, sex, diabetes mellitus, NYHA class, rest dyspnoea, current cigarette smoking, previous hospitalisation for heart failure, first diagnosis of heart failure over 2 years ago, previous myocardial infarction, atrial fibrillation, heart rate, diastolic blood pressure, dependent oedema, pulmonary crackles, cardiomegaly, pulmonary oedema, mitral regurgitation, and candesartan treatment, using a multivariable Cox proportional hazards model. A 2-tailed p value of less than 0.05 was considered statistically significant. Data from the two studies of patients with reduced LVEF were combined, as this group was prespecified as clinically important. For combined analysis of the three trials, statistical heterogeneity tests were performed for each endpoint. To identify the independent predictors of bronchodilator prescribing, a logistic regression model was employed with demographic and disease-related characteristics as potential predictors.

7.3 Results

7.3.1 Baseline characteristics

The findings from 7599 patients were analysed. The median duration of follow-up was 37.7 months. A detailed review of patients' baseline characteristics has previously been published.[354] The baseline characteristics of patients receiving bronchodilators are displayed in Table 7.1. 674 patients (8.9%) were prescribed bronchodilators. The prevalence was similar in patients with reduced compared with preserved systolic function (respectively 8.7% vs 9.2%, p=0.46).

Overall, a prior smoking history was more frequent in patients receiving bronchodilators (59.8% vs 47.7%, p<0.0001), although the proportion of current smokers was similar (16.2% vs 14.5%, p=0.24). No significant difference was observed in cardiovascular comorbidity between those prescribed and not prescribed bronchodilators, including history of myocardial infarction, angina, stroke, diabetes, hypertension and atrial fibrillation. A greater proportion of patients receiving bronchodilators had previously been hospitalised for worsening HF (77.7% vs 70.8%, p=0.0001). These findings were consistent irrespective of reduced or preserved ejection fraction.

Patients prescribed bronchodilators had poorer functional status, as indicated by an increased prevalence of NYHA classification III to IV. Overall, and in the reduced and preserved systolic function groups, clinical signs of HF were more common in those receiving bronchodilators. These included elevated jugular venous pressure, peripheral oedema, pulmonary crepitations and wheeze. Mean ejection

fraction was however similar comparing those with and without bronchodilators (Overall 39.8% vs 38.8% respectively, p=0.10).

Table 7.1 Baseline characteristics of patients receiving bronchodilators

Characteristics	Preserved LVEF n=3023		Reduced LVEF n=4576		Overall n=7599	
Mean (SD) or n (%)	Bronchodilator n=277 (9.2)	No Bronchodilator n=2746 (90.8)	Bronchodilator n=397 (8.7)	No Bronchodilator n=4179 (91.3)	Bronchodilator n=674 (8.9)	No Bronchodilator n=6925 (91.1)
Demographics						
Age (years)	67.7 (10.5)	66.6 (11.1)	66.5 (9.8)	64.5 (11.1)	67.0 (10.1)	65.3 (11.1)
Female Sex	116 (41.9)	1096 (39.9)	27.8 (5.5)	27.6 (5.1)	208 (30.9)	2192 (31.7)
BMI	30.4 (7.1)	29.0 (5.6)	92 (23.2)	1096 (26.2)	28.9 (6.3)	28.2 (5.3)
Smoking Status						
Current Smoker	37 (13.4)	372 (13.5)	72 (18.1)	633 (15.1)	109 (16.2)	1005 (14.5)
Previous Smoker	151 (54.5)	1221 (44.5)	252 (63.5)	2080 (49.8)	403 (59.8)	3301 (47.7)
Non Smoker	89 (32.1)	1153 (42.0)	73 (18.4)	1466 (35.1)	162 (24.0)	2619 (37.8)
Medical History						
Myocardial Infarction	111 (40.1)	1229 (44.8)	230 (57.9)	2434 (58.2)	341 (50.6)	3663 (52.9)
Angina	163 (58.8)	1654 (60.2)	234 (58.9)	2301 (55.1)	397 (58.9)	3955 (57.1)
Stroke	23 (8.3)	245 (8.9)	36 (9.1)	359 (8.6)	59 (8.8)	604 (8.7)
Hypertension	184 (66.4)	1759 64.1)	202 (50.9)	2041 (48.8)	386 (57.3)	3800 (54.9)
Diabetes Mellitus	91 (32.9)	766 (27.9)	116 (29.2)	1190 (28.5)	207 (30.7)	1956 (28.2)
Atrial Fibrillation	85 (30.7)	796 (29.0)	114 (28.7)	1088 (26.0)	199 (29.5)	1884 (27.2)
Prior HF hospitalisation	212 (76.5)	1864 (67.9)	312 (78.6)	3038 (72.7)	524 (77.7)	4902 (70.8)
Cancer	31 (11.2)	195 (7.1)	34 (8.6)	253 (6.1)	65 (9.6)	448 (6.5)
Severity Markers						
Ejection Fraction	55.6 (10.1)	53.9 (9.3)	28.8 (7.6)	28.8 (7.5)	39.8 (15.8)	38.8 (14.8)
NYHA II	113 (40.8)	1723 (62.7)	113 (28.5)	1467 (35.1)	226 (33.5)	3190 (46.1)
NYHA III	157 (56.7)	983 (35.8)	259 (65.2)	2586 (61.9)	416 (61.7)	3569 (51.5)
NYHA IV	7 (2.5)	40 (1.5)	25 (6.3)	126 (3.0)	32 (4.7)	166 (2.4)
Physical Examination						
Heart Rate (bpm)	75.4 (12.7)	70.9 (12.4)	76.9 (13.2)	73.6 (13.3)	76.3 (13.0)	72.5 (13.0)
Systolic BP (mm Hg)	134.8 (18.3)	136.3 (18.5)	127.1 (18.6)	127.4 (18.8)	130.3 (18.9)	130.9 (19.2)
Diastolic BP (mm Hg)	77.3 (11.0)	77.9 (10.7)	74.2 (11.0)	76.0 (10.7)	75.5 (11.1)	76.7 (10.7)
Elevated JVP	111 (40.1)	955 (34.8)	149 (37.5)	1393 (33.3)	260 (38.6)	2348 (33.9)
Peripheral Oedema	83 (30.0)	752 (27.4)	98 (24.7)	921 (22.0)	181 (26.9)	1673 (24.2)
Pulmonary Crepitations	72 (26.0)	418 (15.2)	87 (21.9)	655 (15.7)	159 (23.6)	1073 (15.5)
Pulmonary Wheeze	30 (10.8)	51 (1.9)	49 (12.3)	100 (2.4)	79 (11.7)	151 (2.2)
Electrocardiogram						
Atrial Fibrillation	43 (15.5)	435 (15.8)	61 (15.4)	609 (14.6)	104 (15.4)	1044 (15.1)
Bundle Branch Block	50 (18.1)	384 (14.0)	141 (35.5)	1236 (29.6)	191 (28.3)	1620 (23.4)
Chest X-Ray						
Pulmonary Oedema	8 (2.9)	74 (2.7)	11 (2.8)	118 (2.8)	19 (2.8)	192 (2.8)
Cardiomegaly	55 (19.9)	439 (16.0)	115 (29.0)	1058 (25.3)	170 (25.2)	1497 (21.6)
Concomitant Therapy						
β-blocker	90 (32.5)	1594 (58.0)	125 (31.5)	2394 (57.3)	215 (31.9)	3988 (57.6)
• Carvedilol	10(3.6)	194(7.1)	34(8.6)	742(17.8)	44(6.5)	936(13.5)
• Metoprolol	37(13.4)	734(26.7)	50(12.6)	1124(26.9)	87(12.9)	1858(26.8)
• Bisoprolol	9(3.2)	126(4.6)	8(2.0)	142(3.4)	17(2.5)	268(3.9)
• Atenolol	23(8.3)	339(12.4)	19(4.8)	219(5.2)	42(6.2)	558(8.1)
• Other β-blocker	11(4.0)	205(7.5)	15(3.8)	172(4.1)	26(3.9)	377(5.4)
Calcium channel blocker	119 (43.0)	825 (30.0)	70 (17.6)	528 (12.6)	189 (28.0)	1353 (19.5)
Amiodarone	32 (11.6)	214 (7.8)	60 (15.1)	457 (10.9)	92 (13.6)	671 (9.7)
Digoxin	86 (31.0)	756 (27.5)	225 (56.7)	2187 (52.3)	311 (46.1)	2943 (42.5)
ACE inhibitors	45 (16.2)	531 (19.3)	210 (52.9)	2339 (56.0)	255 (37.8)	2870 (41.4)
Spironolactone	43 (15.5)	309 (11.3)	91 (22.9)	829 (19.8)	134 (19.9)	1138 (16.4)
Diuretics	232 (83.8)	2027 (73.8)	366 (92.2)	3661 (87.6)	598 (88.7)	5688 (82.1)

β-blocker utilisation was markedly lower in patients receiving bronchodilators compared to those without bronchodilator therapy: Overall 31.9% vs 57.6%; Reduced 31.5% vs 57.3%; Preserved 32.5% vs 58.0% (all p<0.0001). The proportion of patients receiving a β-1 selective adrenoceptor blocker (metoprolol, bisoprolol or atenolol) was similar in patients with and without bronchodilators (67.9% vs 67.3%, p=0.85). The use of amiodarone, digoxin and calcium channel blockers was greater in those receiving bronchodilators, both overall and in patients with reduced or preserved ejection fraction. Treatment with bronchodilators was also associated with greater use of diuretic therapy, including spironolactone.

7.3.2 Independent predictors of use of bronchodilator therapy

Multivariable analysis of predictors of bronchodilator prescribing revealed smoking history to be the strongest independent determinant (Table 7.2).

Table 7.2 Independent predictors of bronchodilator use for CHARM overall

Predictor	Odds Ratio (95% CI)	p value	Wald Chi
Non-smoker	0.47 (0.39-0.56)	<0.0001	62.7
Heart rate (per 10 bpm)	1.25 (1.18-1.32)	<0.0001	56.6
Age	1.03 (1.02-1.03)	<0.0001	39.9
BMI	1.04 (1.02-1.05)	<0.0001	21.2
Diastolic blood pressure	0.99 (0.98-1.00)	0.0018	9.8
Ischaemic heart disease	0.81 (0.68-0.96)	0.0131	6.2

After adjusting for baseline variables including demographics, aetiology of heart failure and medical history, the odds of receiving bronchodilators for smokers were approximately twice those for non-smokers (odds ratio 0.47 [0.39-0.56],

p<0.0001). Age, body mass index, heart rate, blood pressure and presence of ischaemic heart disease were also independent predictors of bronchodilator use.

7.3.3 Mortality

Bronchodilator therapy was independently associated with increased mortality. 32.6% of patients receiving bronchodilators died from any cause, compared with 23.3% of those without bronchodilators (Table 7.3).

Table 7.3 Association between bronchodilator therapy and clinical outcomes by systolic function

Outcomes/ Systolic Function	Bronchodilator n=674	No Bronchodilator n=6925	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value	p value interaction *
Cardiovascular death or HF hospitalisation							
Overall	303 (45.0)	2157 (31.1)	1.65 (1.47-1.87)	<0.0001	1.38 (1.22-1.56)	<0.0001	0.1452
Reduced LVEF	198 (49.9)	1563 (37.4)	1.52 (1.31-1.76)	<0.0001	1.32 (1.14-1.53)	0.0003	
Preserved LVEF	105 (37.9)	594 (21.6)	2.00 (1.62-2.46)	<0.0001	1.52 (1.22-1.89)	0.0002	
All cause mortality							
Overall	220 (32.6)	1611 (23.3)	1.53 (1.33-1.76)	<0.0001	1.26 (1.09-1.45)	0.0015	0.4485
Reduced LVEF	155 (39.0)	1195 (28.6)	1.49 (1.26-2.12)	<0.0001	1.27 (1.07-1.51)	0.0055	
Preserved LVEF	65 (23.5)	416 (15.1)	1.63 (1.26-2.12)	0.0002	1.26 (0.95-1.65)	0.1041	
Non cardiovascular death							
Overall	51(7.6)	320(4.6)	1.78(1.32-2.39)	0.0001	1.49(1.10-2.01)	0.0097	0.4383
Reduced LVEF	31(7.8)	199(4.8)	1.81(1.24-2.64)	0.0021	1.57(1.07-2.31)	0.0214	
Preserved LVEF	20(7.2)	12(4.4)	1.73(1.08-2.78)	0.0231	1.35(0.82-2.22)	0.2394	
Cardiovascular death							
Overall	169 (25.1)	1291 (18.6)	1.47 (1.25-1.72)	<0.0001	1.21 (1.03-1.42)	0.0216	0.7738
Reduced LVEF	124 (31.2)	996 (23.8)	1.43 (1.18-1.72)	0.0002	1.22 (1.01-1.47)	0.0412	
Preserved LVEF	45 (16.2)	295 (10.7)	1.59 (1.16-2.18)	0.0038	1.23 (0.89-1.71)	0.2171	
Death due to HF progression							
Overall	66 (9.8)	403 (5.8)	1.84 (1.42-2.38)	<0.0001	1.40 (1.07-1.82)	0.0128	0.6735
Reduced LVEF	49 (12.3)	318 (7.6)	1.77 (1.31-2.39)	0.0002	1.39 (1.03-1.89)	0.0328	
Preserved LVEF	17 (6.1)	85 (3.1)	2.08 (1.23-3.50)	0.0059	1.51 (0.86-2.64)	0.1526	
Sudden death							
Overall	66 (9.8)	577 (8.3)	1.29 (1.00-1.66)	0.0532	1.13 (0.87-1.46)	0.3474	0.1283
Reduced LVEF	47 (11.8)	462 (11.1)	1.17 (0.87-1.58)	0.3105	1.06 (0.78-1.43)	0.7094	
Preserved LVEF	19 (6.9)	115 (4.2)	1.72 (1.06-2.79)	0.0292	1.34 (0.81-2.22)	0.2594	
HF hospitalisation							
Overall	225 (33.4)	1450 (20.9)	1.81 (1.57-2.09)	<0.0001	1.49 (1.29-1.72)	<0.0001	0.5480
Reduced LVEF	142 (35.8)	1016 (24.3)	1.66 (1.40-1.98)	<0.0001	1.43 (1.20-1.71)	0.0001	
Preserved LVEF	83 (30.0)	434 (15.8)	2.14 (1.69-2.71)	<0.0001	1.59 (1.25-2.04)	0.0002	
CV death, HF hospitalisation, non-fatal MI, non-fatal stroke							
Overall	317 (47.0)	2372 (34.3)	1.57 (1.39-1.76)	<0.0001	1.32 (1.17-1.76)	<0.0001	0.2775
Reduced LVEF	205 (51.6)	1667 (39.9)	1.47 (1.27-1.70)	<0.0001	1.28 (1.10-1.48)	0.0010	
Preserved LVEF	112 (40.4)	705 (25.7)	1.78 (1.46-2.17)	<0.0001	1.43 (1.16-1.76)	0.0007	

* Interaction between bronchodilator (vs no bronchodilator) and reduced LVEF (vs preserved LVEF)

After adjusting for additional predictors of mortality, the risk of death was 26% higher in patients prescribed bronchodilators (adjusted HR 1.26 [95% CI 1.09–1.45]). This higher risk of overall mortality reflected a higher incidence of both non-cardiovascular death (7.6% vs 4.6%, HR 1.49 [1.10-2.01]) and cardiovascular death (25.1% vs 18.6%, HR 1.21 [1.03-1.42]). The higher risk of cardiovascular death was largely attributable to death due to progressive pump failure (9.8% vs 5.8%, HR 1.40 [1.07-1.82]). The risk of sudden death was not elevated after correcting for baseline differences between patients receiving and not receiving bronchodilators. The greater mortality associated with bronchodilator use was consistent in patients with reduced and preserved systolic function: all cause mortality (HR 1.27 vs 1.26 respectively); cardiovascular death (HR 1.22 vs 1.23); and non-cardiovascular death (HR 1.57 vs 1.35).

7.3.4 Cardiovascular morbidity and mortality

Bronchodilator therapy was an independent predictor of worse fatal and non-fatal cardiovascular outcomes in patients with heart failure (Table 7.3). Overall, the primary outcome of cardiovascular death or HF hospitalisation occurred in 45.0% patients receiving bronchodilators as opposed to 31.1% of those without bronchodilators (adjusted HR 1.38 [1.22-1.56], $p<0.0001$, Table 7.3). The risk of hospitalisation due to worsening HF associated with bronchodilators was likewise 49% higher (HR 1.49 [1.29-1.72], $p<0.0001$). Finally, the relative risk of sustaining a major adverse cardiovascular event (defined as cardiovascular death, HF hospitalisation, non-fatal MI or non-fatal stroke) was 32% higher in those receiving bronchodilators (HR 1.32 [1.17-1.76], $p<0.0001$).

As with mortality, the association between bronchodilator therapy and adverse outcomes was consistent in patients with reduced and preserved systolic function. Risk of the primary endpoint, HF hospitalisation, and major adverse cardiovascular events was greater in patients receiving bronchodilators, irrespective of left ventricular ejection fraction. Formal statistical testing for an interaction confirmed no significant difference between the cohorts (Table 7.3).

7.3.5 Interaction between bronchodilators and concurrent β-blockers

Bronchodilator use was associated with adverse outcomes regardless of concurrent β-blocker therapy (Table 7.4).

Table 7.4 Association between bronchodilator use and clinical outcomes according to background β-blocker therapy in CHARM overall

Outcome, β-blocker	Bronchodilator	No Bronchodilator	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value	p value interaction *
Cardiovascular death or HF hospitalisation							
β-blocker	85 (39.5)	1054 (26.4)	1.73 (1.39-2.16)	0.0000	1.44 (1.15-1.80)	0.0015	0.2557
No β-blocker	218 (47.5)	1103 (37.6)	1.22 (1.05-1.42)	0.0080	1.22 (1.05-1.42)	0.0080	
All cause mortality							
β-blocker	61 (28.4)	773 (19.4)	1.62 (1.25-2.10)	0.0003	1.32 (1.01-1.72)	0.0406	0.3804
No β-blocker	159 (34.6)	838 (28.5)	1.14 (0.96-1.36)	0.1282	1.14 (0.96-1.36)	0.1282	
Non cardiovascular death							
β-blocker	15 (7.0)	153 (3.8)	1.99 (1.17-3.38)	0.0112	1.48(0.86-2.55)	0.1547	0.5878
No β-blocker	36 (7.8)	167 (5.7)	1.39 (0.96-2.01)	0.0798	1.19(0.78-2.32)	0.1543	
Cardiovascular death							
β-blocker	46 (21.4)	620 (15.5)	1.52 (1.13-2.06)	0.0059	1.26 (0.93-1.71)	0.1318	0.4942
No β-blocker	123 (26.8)	671 (22.8)	1.09 (0.90-1.33)	0.3629	1.09 (0.90-1.33)	0.3629	
Death due to HF progression							
β-blocker	15 (7.0)	161 (4.0)	1.94 (1.14-3.29)	0.0143	1.56 (0.91-2.69)	0.1064	0.4301
No β-blocker	51 (11.1)	242 (8.2)	1.19 (0.87-1.62)	0.2738	1.19 (0.87-1.62)	0.2738	
Sudden death							
β-blocker	24 (11.2)	297 (7.4)	1.65 (1.09-2.51)	0.0178	1.46 (0.96-2.23)	0.0772	0.1181
No β-blocker	42 (9.2)	280 (9.5)	0.93 (0.67-1.29)	0.6752	0.93 (0.67-1.29)	0.6752	
HF hospitalisation							
β-blocker	61 (28.4)	696 (17.5)	1.87 (1.44-2.43)	0.0000	1.55 (1.19-2.02)	0.0013	0.3402
No β-blocker	164 (35.7)	754 (25.7)	1.30 (1.10-1.54)	0.0027	1.30 (1.10-1.54)	0.0027	
Cardiovascular death, HF hospitalisation, non-fatal MI, non-fatal stroke							
β-blocker	89 (41.4)	1187 (29.8)	1.60 (1.29-1.98)	0.0000	1.33 (1.07-1.65)	0.0115	0.4781
No β-blocker	228 (49.7)	1185 (40.3)	1.19 (1.03-2.51)	0.0154	1.19 (1.03-1.38)	0.0154	

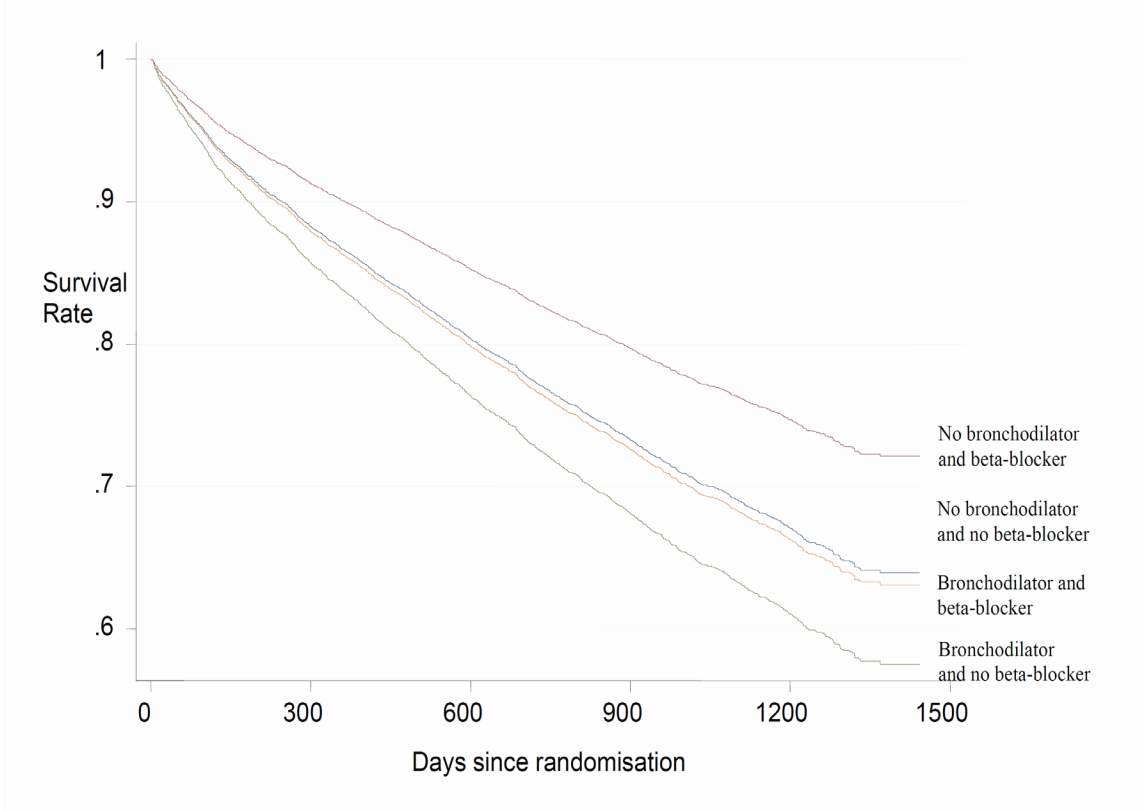
* Interaction between bronchodilator (vs no bronchodilator) and β-blocker (vs no β-blocker)

Among patients receiving β-blockers, bronchodilator use (compared to no bronchodilator use) was associated with greater all cause mortality (HR 1.32 [1.01-1.72] versus 1.14 [0.96-1.36] in those not receiving a β-blocker), cardiovascular death or HF hospitalisation (HR 1.44 [1.15-1.80] versus 1.22 [1.05-1.42]), and major adverse cardiovascular events (HR 1.33 [1.07-1.65] versus 1.19 [1.03-1.38]). No statistical interaction was observed between bronchodilator therapy and β-blockade with respect to any pre-specified outcome.

7.3.6 Relationship between β-blockers and mortality

Mortality was significantly lower in patients receiving β-blockers, irrespective of concurrent bronchodilator therapy (Figure 7.1).

Figure 7.1 Adjusted survival rate by bronchodilator and β-blocker use



Overall, the adjusted hazard ratio for mortality comparing patients with and without β-blockade was 0.77 [0.70–0.85], p<0.001. In patients receiving bronchodilators, 28.4% of those prescribed β-blockers died, compared to 34.6% of those not prescribed β-blockers (HR 0.87 [0.64-1.18], p=0.354). This relative risk of death in β-blocker treated patients was also lower in those not receiving bronchodilators (19.4% vs 28.5% respectively, HR 0.76 [0.69-0.85], p<0.001). No interaction was observed between β-blockade and bronchodilator therapy.

7.4 Discussion

Although the association between bronchodilator use (both β-agonist and anticholinergic) and adverse cardiovascular events in patients with pulmonary disease is well recognised,[234,235,247,251,351] the relationship between the use of these drugs and outcomes in patients with HF is uncertain.[248,249] Several findings were noteworthy. Bronchodilator use was associated with increased all cause mortality, cardiovascular death, HF hospitalisation and major adverse cardiovascular events. The adverse prognostic implications were consistent in patients with reduced and preserved systolic function, and remained significant after comprehensive multivariate adjustment. Moreover, the magnitude of risk associated with bronchodilators was comparable to recognised predictors such as NYHA class, bundle branch block, ischaemic heart disease, heart rate and blood pressure.[355] No interaction was observed between bronchodilators and β-blockade with respect to outcomes.

Remarkably few reports describe bronchodilator use in patients with HF. The prevalence in CHARM Overall (8.9%) was similar to that observed in a community heart failure clinic in the United Kingdom (12.1%).[172] Although pulmonary disease is more common in patients with HF and preserved ejection fraction,[1] the prevalence of bronchodilator use was similar in patients with reduced and preserved systolic function. Symptoms and signs of HF were more frequent in patients prescribed bronchodilators despite similar ejection fractions, as were prior hospitalisations for decompensated HF. The findings highlight the diagnostic dilemmas posed by the combination of HF and pulmonary disease.[1] No qualitative symptoms are unique to HF.[8] Signs are equally misleading. Although cor pulmonale is rare in patients with COPD,[1,137,138] elevated jugular venous pressure is not. A comprehensive study investigated 405 elderly patients with stable COPD.[137] Heart failure was diagnosed by an expert panel following chest radiography, electrocardiography, echocardiography and pulmonary function tests. Nearly a quarter (23.3%) of the 322 patients with COPD in whom HF was excluded had a raised jugular venous pressure.[18] A similar proportion of patients with COPD are reported to have mild pulmonary hypertension.[138] Pulmonary disease therefore appears to worsen the clinical syndrome of HF.

The diversity and magnitude of adverse outcomes associated with bronchodilator therapy is surprising. Cohorts defined by bronchodilator prescription undoubtedly represent a heterogeneous group of patients: COPD, asthma, restrictive lung disease, and those misdiagnosed with airflow obstruction. The latter is common in patients with decompensated HF,[45,46] in whom interstitial oedema causes airway compression and bronchial hyperresponsiveness.[1,47] Non-cardiovascular deaths are

inevitable in cohorts dominated by pulmonary disease. The excess cardiovascular mortality is more concerning. Bronchodilators were associated with a 40% higher risk of death due to progressive pump failure. The risk of hospitalisation for worsening HF was likewise 49% greater.

These findings corroborate and extend two prior studies examining patients with HF or LVSD prescribed inhaled β-agonists.[248,249] In 1529 subjects with LVSD identified retrospectively through imaging records,[249] all cause mortality and HF hospitalisation within 1 year increased with the average number of canisters dispensed per month. After covariate adjustment, the risk of HF admission was: 1.3 [0.9-2.0] (1 canister / month); 1.7 [1.2-2.5] (2 canisters / month); 2.0 [1.3-3.0] (≥ 3 canisters / month). Risk of death was similarly increased: 0.9 [0.5-1.6] (1 canister / month); 1.4 [0.9-2.2] (2 canisters / month); 2.0 [1.3-3.2] (≥ 3 canisters / month). However, the association was undermined by the indication for β-agonist use: increasing dyspnoea and resulting β-agonist prescription may simply have reflected worsening HF. Without markers of HF severity the multivariate model was unable to adjust for such confounding. A second case control study observed a similar relationship between β-agonists and HF hospitalisation in patients with existing HF.[248] The risk remained significant after adjustment for age, cardiovascular comorbidity, presence of COPD and β-blocker prescription (OR 1.6 [1.0-2.7]).

The association between bronchodilators and worsening HF could be attributed to confounding by indication and the severity of underlying lung disease. Bronchodilators may simply be prescribed to patients with worse heart failure or airflow obstruction. However, unlike previous studies, the former confounder (severity of heart failure) is minimised by comprehensive adjustment incorporating

measures of heart failure signs, symptoms and functional class as well as history of heart failure hospitalisation and ejection fraction. The latter confounder (severity of lung disease) is to some extent addressed in the current analysis as the CHARM enrolment criteria excluded patients with 'severe obstructive pulmonary disease'. Furthermore, the recruitment bias inherent to clinical trials is also likely to have reduced inclusion of individuals with severe pulmonary disease. Nonetheless, infection is a recognised precipitant of HF decompensation and may have contributed to the marked increase in fatal and non-fatal pump failure.[78,86]

Heart failure is characterised by increased adrenergic drive. β_1 and β_2 adrenoceptors mediate noradrenaline toxicity, fibrosis and necrosis. Down regulation of β_1 receptors with preservation of the β_2 subpopulation reduces the β_1/β_2 ratio.[231] The inotropic responsiveness (and likewise vulnerability) of the failing myocardium to β_2-agonists thereby assumes greater importance.[232,233] Although the specific types and doses of bronchodilator were not recorded, inhaled β_2-agonists are baseline therapy for both COPD and asthma. It is possible that bronchodilators compound maladaptive remodeling and further depress myocardial function. Two observations temper this argument. β_2-agonists exert numerous arrhythmic effects: tachycardia, hypokalaemia, QTC prolongation, disturbed autonomic modulation and depressed heart rate variability.[234-237] The lack of an associated increase in sudden cardiac death, particularly in those with LVSD, suggests systemic consequences are minimal. Secondly, if mediated by β-adrenergic stimulation, the adverse consequences would possibly be lessened by concurrent β-blocker use. No such interaction was observed. However, the majority of patients received cardioselective

β_1-blockers, namely metoprolol or bisoprolol. Whether β_1-blockade antagonises β_2-mediated effects is unknown.

In three observational studies, β-blockers were consistently associated with better survival in patients with HF and concurrent COPD.[128,166,227] None reported the outcomes of patients receiving bronchodilators, in whom physicians may be wary of β-blockade. This important patient group has now been examined. Although limited by patient numbers, formal testing revealed no significant interaction between bronchodilator use and the better survival associated with β-blockade. Moreover, no adverse effects were observed for any prespecified endpoint. In particular, non-cardiovascular mortality was not increased in patients taking bronchodilators who were also receiving β-blockers. This observation should help alleviate historical concerns regarding safety. As with previous reports,[128,166,227] recruitment bias and the absence of pulmonary function data limit inference to patients with severe or reversible airflow obstruction.

Several limitations must be acknowledged. Whether bronchodilators were prescribed for COPD, asthma, or alternative reasons is unknown. The specific types, administration routes and doses of bronchodilator were not recorded. However, inhaled short acting β-agonists are recommended first line therapy.[5] Although the prevalence of β-agonists (particularly oral), anticholinergics and inhaled corticosteroids would be interesting, concurrent prescribing would inextricably merge their respective effects. Finally, as with all observational studies, no causal relationship may be inferred.

7.5 Conclusion

Bronchodilator use is a powerful independent predictor of worsening heart failure and increased mortality in a broad spectrum of patients with HF. Whether this relates to a toxic effect of β-agonists (or other bronchodilators), underlying pulmonary disease or both is unclear. There is a simple clinical message. Vigilance is paramount when considering the prescription of bronchodilators in patients with HF. Physicians should be rigorous in their diagnosis of airways disease, obtain objective evidence of airflow obstruction and do so when patients are clinically euvolaemic. β-agonists should only be prescribed in patients where these agents lead to documented reversal of airways obstruction. Physicians should also be alert to the fact that use of bronchodilators identifies a patient at increased risk of worsening heart failure and death. There are many challenges for future research. The interaction between bronchodilators, pulmonary disease, and the syndrome of heart failure is complex. Greater understanding of these relationships may in turn explain the association between bronchodilators, hospital admissions and increased mortality. Only randomised controlled trials can conclusively prove or disprove the safety of bronchodilators in patients with heart failure.

Chapter 8

Final Discussion

Heart failure and chronic obstructive pulmonary disease are common partners with common problems. Each condition affects in excess of ten million patients worldwide.[4,5] Reports addressing this intersection between cardiology and respiratory medicine are however few and far between. The demise of the general physician and evolution of subspecialty medicine is partly responsible. Cardiologists increasingly practice in tertiary centres devoid of other specialties. Ironically, as we move towards single system medicine, the aging population presents with increasing comorbidities.

Landmark clinical trials have transformed the treatment and prognosis of patients with HF. ACE inhibitors, β-blockers, aldosterone antagonists, angiotensin receptor blockers and device therapies all confer unequivocal morbidity and mortality benefits.[4] With each advance the absolute survival gains of novel therapies in clinical trials has diminished. Despite this armamentarium, prognosis at the population level remains poor.[275] Two issues predominate: limited uptake of evidence based therapies into clinical practice, and the impact of comorbidities. Heart failure is characterised by the latter: diabetes, COPD, anaemia, chronic kidney disease, atrial fibrillation and coronary disease. Each condition is independently associated with worse clinical outcomes, through mechanisms which remain incompletely defined. Whether established therapies for each condition are beneficial in patients with concurrent HF is often uncertain.

Unlike other comorbidities, the coexistence of COPD exposes the patient to double jeopardy. In addition to therapeutic dilemmas, the combination poses many diagnostic challenges. These are comprehensively and critically appraised in this thesis. Such review will hopefully prove useful to practicing physicians. A number

of simple conclusions may be drawn. Symptoms and signs frequently overlap, as highlighted in the CHARM and VALIANT analyses. The evaluation of cardiac and pulmonary function is often problematic and potentially misleading. Echocardiography and pulmonary function tests should be performed in every patient with HF and suspected COPD. Careful interpretation is required to avoid misdiagnosis and inappropriate treatment. In particular, airflow obstruction must be demonstrated when the patient is euvolaemic, assessed by clinical signs (pitting oedema, elevated jugular venous pressure, pulmonary rales) and chest radiograph. Very high and very low concentrations of natriuretic peptides have high positive and negative predictive values for diagnosing HF in those with both conditions. Intermediate values are less informative. In those with limited acoustic windows cardiac magnetic resonance imaging is the modality of choice.

The epidemiology of HF and COPD was previously ill defined. This thesis has created a comprehensive reference source expanding more narrative publications. The information allows comparison of the prevalence of COPD in different environments, between countries, and to a degree over time. The analysis from the Scottish Continuous Morbidity Recording scheme confirms and extends these observations. The prevalence of COPD was approximately sevenfold greater in patients with HF than in the primary care population. More importantly, the prevalence increased year on year. These changes may previously have been attributed to an ageing population or increasing age of presentation. However, the trend remained significant after age standardisation. Finally, I observed a clear socioeconomic gradient, with prevalence greatest in the most deprived. Smoking, the main risk factor for COPD, increased in parallel. HF and COPD are clearly

'common partners'. The results emphasise the need to promote smoking cessation, and target the most deprived patients with HF.

The 'common problems' are both therapeutic and prognostic. The former undoubtedly contributes to the latter. The cornerstones of therapy are β-blockers and β-agonists, whose pharmacologic effects are diametrically opposed. Each is purported to adversely affect the alternative condition. β-blockers are well tolerated in patients with mild and fixed airflow obstruction. Although patients with more severe disease may tolerate β-blockers, the evidence is rudimentary.[2] Critical appraisal revealed several shortcomings, foremost being that no study had included patients with HF. Of the 20 randomised controlled trials included in the Cochrane meta-analysis, 11 involved single doses and only one lasted longer than a month. The long term impact of β-blockade on pulmonary function, symptoms and quality of life was therefore largely unknown. In particular, the effect on health status had never been assessed in any cohort with COPD.

Although recruitment was challenging, the baseline characteristics of the cohort were well matched and consistent with previous studies in moderate to severe COPD. Three key findings emerged. Treatment with bisoprolol was associated with an increase in airflow obstruction. However, bronchodilator response to inhaled β_2-agonist was preserved. β-blockade exerted no adverse effect on health related quality of life or functional status. The primary endpoint initially appears at odds with the Cochrane analysis, which observed no significant change in FEV_1 with longer term cardioselective β-blockade (–2.39% [CI –5.69% to 0.91%]).[2] However, the trials included in the meta-analysis exhibited a degree of heterogeneity. In the longest study of patients with severe COPD, atenolol and metoprolol each significantly

reduced FEV_1 by around 10% over four weeks.[195] I observed a reduction in FEV_1 of similar magnitude (post-bronchodilator 110 ml, 7%). A further randomised cross-over trial supports my findings, though was not included in the meta-analysis.[201] FEV_1 declined significantly over 6 months by approximately 0.2 litres in patients with mild COPD and significant reversibility receiving bisoprolol or atenolol. Although lacking a concurrent placebo group, lung function parameters normalised during the placebo cross-over period, suggesting β-blockade directly caused bronchoconstriction. Furthermore, airway resistance increased with therapy duration despite unchanged β-blocker doses. This highlights the need for longer term studies, particularly in patients with HF.

The finding of preserved β_2-agonist response corroborates two prior single dose studies of bisoprolol in patients with mild to moderate COPD.[190,191] Bisoprolol is highly β_1-selective, providing a wide split between β_1 and β_2-adrenoceptor blockade. At therapeutic levels, response to β_2-agonists appears largely preserved and counteracts any change in airway resistance. This is particularly important in patients with HF, in whom abrupt β-blocker withdrawal may precipitate rebound ischaemia, ventricular arrhythmias and even death. The ability to treat bronchospasm while continuing or reducing the dose of β_1-blockade is reassuring.

The assessment of health status was likewise encouraging. Most importantly, β-blockade exerted no adverse effect on health related quality of life or functional status. Secondly, all three measures of health status and components including dyspnoea score improved. Though not statistically significant, the consistent directionality of change is reassuring. Finally, the observations were concordant with the stable residual volume, which predicts exercise capacity better than FEV_1.

The findings pose further questions and hopefully provide direction for larger randomised controlled trials. Is an asymptomatic reduction in FEV_1 an acceptable sacrifice given the established prognostic benefits of β-blockers? Will symptoms and quality of life improve significantly over longer follow up? Are the effects of β-blockade on airflow obstruction and reversibility dose dependent? Only robust multicentre trials will provide the answers.

This paucity of existing evidence translates into clinical practice. Pulmonary disease was the most powerful independent predictor of β-blocker underutilisation in the Euro Heart Failure Survey (OR 0.35).[173] My analysis from the Continuous Morbidity Recording scheme revealed similar odds of β-blocker prescribing in primary care (OR 0.30). Whether the gap between patients with and without COPD is improving was previously unknown. The results were disappointing. Despite the overall improvement, the relative difference between those with and without COPD remained unchanged. By 2004, only 18% of individuals with HF and COPD were prescribed β-blockers in the community. A decade after landmark β-blocker trials, it is remarkable that the Quality and Outcomes Framework in the United Kingdom fails to incorporate β-blockade. The inclusion of β-blocker targets in the framework for 2009/10 will hopefully improve utilisation in those with concurrent COPD. The subject certainly merits revisiting in future.

The Achilles heel of β-blockade in HF with COPD is the lack of proven prognostic benefit. The only contemporary evidence derives from the Val-HeFT trial. Mortality in patients with HF and COPD was approximately 17% in those prescribed β-blockers, as opposed to 31% in those without β-blockade.[128] No statistical adjustment for baseline differences was performed. The analyses from

VALIANT and CHARM build on this report. 51% of patients with concurrent COPD in VALIANT received β-blockers, with an associated lower mortality (25% vs 35%, $p<0.001$). No significant interaction was observed between COPD and β-blocker use with respect to mortality. β-blocker use was not adversely associated with any pre-specified outcome in patients with COPD, including non-cardiovascular mortality. Likewise in CHARM, mortality was significantly lower in patients receiving β-blockers irrespective of concurrent bronchodilator therapy. Although limited by patient numbers, formal testing revealed no significant interaction between bronchodilator use and the better survival associated with β-blockade. Both analyses must be interpreted cautiously. Recruitment bias and the absence of pulmonary function data limit inference to patients with severe or reversible airflow obstruction. Association must never be mistaken for causation. Nevertheless, the findings support the use of β-blockers in patients with HF and COPD.

The short and long term effects of β-blockade contrast markedly: acute negative inotropy precedes improved left ventricular systolic function. β-agonists exert the reverse pharmacologic effects of β-blockers. It follows that acute positive inotropy may give way to longer term left ventricular systolic dysfunction. Critical appraisal of existing evidence supports this theory. β-agonists were associated with increased mortality and HF hospitalisation in two previous studies involving patients with HF.[248,249] However, the results were undermined by limited adjustment for severity of HF and confounding by indication.

The analysis from CHARM in part addresses these shortcomings. Confounding by severity of HF was minimised by comprehensive adjustment incorporating HF signs, symptoms, functional class and ejection fraction.

Bronchodilator use was associated with increased all cause mortality, cardiovascular death, progressive pump failure, and HF hospitalisation. The adverse prognostic implications were consistent in patients with reduced and preserved systolic function. Moreover, the magnitude of risk associated with bronchodilators was comparable to many recognised predictors of poor outcomes.[355]

The relationship between bronchodilators, pulmonary disease, and the syndrome of heart failure appears complex. Elucidating the risk associated with specific bronchodilators will require large well characterised cohorts to provide sufficient statistical power to assess clinical endpoints. Although bronchodilators are the cornerstone of symptomatic relief, the weight of evidence may eventually sway the balance of risk and benefit. Only randomised controlled trials can conclusively prove or disprove the safety of bronchodilators in patients with HF. In the meantime, physicians should prescribe bronchodilators only when clinically indicated, and be aware that bronchodilator use identifies a patient at increased risk of worsening heart failure and death.

Given the range and magnitude of diagnostic and therapeutic problems, the prognosis of patients with HF and COPD has been remarkably overlooked until recently.[97,128,167,171] Both conditions are systemic disorders with overlapping pathophysiological processes. Following an extensive literature review, I found that COPD was consistently an independent predictor of death and HF hospitalisation when reported in multivariable models. In many models the prognostic significance approached or exceeded that of traditional factors. However, the causes of increased mortality were uncertain.

My analysis from VALIANT characterises the impact of COPD on outcomes in patients with MI complicated by HF or LVSD. Atherosclerotic consequences of chronic systemic inflammation in COPD have been postulated.[139,333,334] COPD was an independent predictor of mortality, largely due to increased non-cardiovascular and sudden death. Although the causes of sudden death are uncertain, numerous substrates for ventricular arrhythmias exist in patients with COPD. The safety of β-agonists in susceptible patients must again be questioned. The proposed atherosclerotic effects of COPD appeared of limited clinical significance. The 58% increased risk of atherosclerotic events was reduced by adjusting in multivariable analyses (HR 0.98 [0.77-1.23]). The independent predictors of MI or stroke were all established cardiovascular risk factors or comorbidity. This reinforces the importance of intensive treatment of existing cardiovascular risk factors and disease in such patients.

In conclusion, this thesis has summarised and extended our understanding of heart failure with concurrent chronic obstructive pulmonary disease. An array of diagnostic and therapeutic dilemmas have been exposed which confront practicing physicians on a daily basis. The right answers require the right questions. Hopefully I have posed the right questions and contributed towards finding the right answers. Only large randomised controlled trials will solve the quandary of β-blockers and β-agonists. Justification for these trials evolves from observational data and smaller prospective studies such as my own. In the meantime, I hope the evidence presented in this thesis will stimulate physicians to re-evaluate the management of patients with HF and COPD.

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