Drug-eluting stents: a study of appropriateness and variations in practice

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For Lynda and my parents

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Summary

1) Background

Drug-eluting stents (DES) reduce in-stent restenosis, hitherto a frequent complication of percutaneous coronary intervention (PCI). Despite the reduction in recurrent symptoms and the need for repeat procedures, only highly selected patient groups with simple coronary lesions were studied in the initial trials, and long-term outcome or safety data were initially limited. The lack of long term data was compounded by reports of late stent thrombosis, potentially threatening the safety of the device. DES are more expensive than bare metal stents (BMS), so there is a significant increase the procedural cost of PCI. The uptake of DES in clinical practice created pressure on healthcare budgets leading to explicit rationing in some countries.

This thesis comprises a programme of original work addressing three related aspects of DES use: DES use in clinical practice (Scotland and internationally), "off-label" use of DES and appropriate use of DES (a modified Delphi consensus study).

2) Drug-eluting stent use in clinical practice

Relatively little was known about the actual application of DES in clinical practice. Anecdotal accounts suggested there were geographical practice variations within Scotland and internationally. Scottish practice was analysed with the aim of determining whether DES use varied between hospitals and operators within the Scottish NHS beyond the influence of clinical factors. In examining international practice the aim was to show whether the adoption and use of DES varied between countries and to determine whether practice changed after the stent thrombosis controversy.

a. Clinical practice variation within Scotland - methods and results

Using data from the Scottish Coronary Revascularisation Registry, multi-level logistic regression analysis was performed, analysing for variations in DES use at hospital, operator and patient level. Overall, DES were used in 47.6% of lesions, but varied between hospitals (range 30.6%-61.8%, χ^2=341.6, p<0.0001). There was significant between-operator variation in the null model. This was attenuated by the addition of hospital as a fixed effect. Nonetheless, the final model demonstrated significant between-operator variability and between-hospital variation, after case-mix adjustment.

b. Drug-eluting stent use internationally - methods and results

This study involved collaboration between centres from four countries with established PCI registries: APPROACH Registry (Alberta, Canada), BWGIC (Belgium), Mayo Clinic PCI Registry (USA) and the Scottish Coronary Revascularisation Registry. Customised graphics software was employed to perform trend analysis examining variations in DES use over time, and by clinical sub-group. 178,504 lesions treated between January 2003 and September 2007 were included. In the Mayo Clinic Registry rapid adoption to a peak of 91% DES use for all lesions by late 2004 was observed. Alberta and Scotland showed delayed adoption with lower peak DES use, respectively 56 and 58% of lesions by early 2006. Adoption of DES in Belgium was more gradual and peak use of 35% lower than other registries. Reductions in DES use were seen in all datasets during 2006, though this varied in absolute and relative terms and by clinical sub-group.

c. Conclusions

Practice variations were found at operator and hospital level within Scotland and between countries internationally. Influences on stent choice in the “real world” are likely to be multi-factorial; on an international level, macro-economic forces exerting their influence through healthcare system regulation, payment systems, level of funding and central control are particularly important. It was also clear from the multilevel study of Scottish practice, however, that a clinical consensus does not exist.

3) "Off-label" use of drug-eluting stents

DES are often used for "off-label" indications, untested in RCTs, where observational studies demonstrate complications are higher when compared to "on-label" use. The aim was to determine whether clinical outcomes differ following DES and BMS implantation in a patient cohort defined by DES "off-label" indications.

a. Methods and results

Patients who underwent coronary stenting for an "off-label" indication between January 2003 and September 2005 in Scotland were included. Clinical outcomes were determined using linkage to national admission and death databases. Propensity scores were calculated using important baseline variables and DES were matched to BMS on a one-to-one basis to provide a fair comparison. The final study population comprised 1,642 well matched patients. Event-free survival was calculated over 24 months using the Kaplan-Meier method. All-cause death was more common following BMS during follow-up. No difference in the rates of MI was noted. Target vessel revascularisation was reduced in patients treated with DES.

b. Conclusions

The largely reassuring findings of this study should be seen in the context of a subsequent growing body of literature also suggesting similar risks for DES and BMS when compared for both on-label and off-label use. Although the benefits of DES were evident, the absolute reduction in TVR was lower than previously demonstrated in RCTs.

4) Appropriate use of drug-eluting stents - a modified Delphi consensus study

Best practice with respect to stent selection during PCI was poorly defined, as evidenced by the lack of detailed clinical guidance on the use of DES and wide

practice variation demonstrated. It was not clear whether in any given setting there had been either underuse - potentially forfeiting the benefits of DES, or overuse - where benefits may be outweighed by risks. The aim was to use an expert panel to develop criteria for the appropriate use of DES using the modified Delphi method, to determine the extent to which current practice in Scotland met the appropriateness criteria and to validate the criteria by analysing clinical outcomes

a. Methods, results, conclusions

Consensus criteria for appropriate DES use were defined using a modified Delphi questionnaire. Expert panelists were used to define levels of appropriate use and were compared to clinical practice. The results suggested that current overall rates of DES use are acceptable. Better targeting of DES to the most appropriate lesions may be possible with the aims of reducing the known geographical inequities and maximising clinical benefit. Finally, using similar methods to chapter 4, it was shown that underuse of DES in appropriate patients was associated with higher levels of target vessel revascularisation without any difference in MI or death.

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Acronyms and abbreviations

ACS Acute coronary syndrome

AHA American heart association

APPROACH Alberta provincial project for outcome assessment in coronary heart disease

ARC Academic research consortium

BASKET Basel stent kosten-effektivitäts trial

BASKET-LATE Basel stent kosten effektivitäts trial - late thrombotic events

BDIC Bayesian deviance information criterion

BMS Bare metal stents

BWGIC Belgian working group on invasive cardiology

CABG Coronary artery bypass grafting

DES Drug-eluting stents

CAD Coronary artery disease

CARDS Cardiology Audit and Registration Data Standards

C-SIRIUS Canadian multicenter, randomized, double-blind study of the sirolimus-coated BS Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions

CI Confidence interval

CTO Chronic total occlusion

D Stent diameter

DIABETES Diabetes and sirolimus-eluting stent trial

ENDEAVOR II Randomized comparison of the Endeavor ABT-578 drug eluting stent with a bare metal stent for coronary revascularization

ESC European society of cardiology

E-SIRIUS European sirolimus-eluting stent in de novo native coronary lesions

FDA Food and drug administration

HR Hazard ratio

HTA Health technology assessment

ICD International classification of diseases

IQR Inter-quartile range

L Stent length

LAD Left anterior descending artery

LCx Left circumflex artery

LMS/LMCA Left main coronary artery

MACE Major adverse cardiovascular events

MCMC Markov chain Monte Carlo

MI Myocardial Infarction

NEJM New England journal of medicine

NICE National institute for health and clinical excellence

NHS National health service

NSTEMI Non-ST elevation myocardial infarction

OPCS Office for Population, Census and Surveys

PASSION Paclitaxel-eluting stent versus conventional stent in ST-Segment Elevation myocardial infarction

PCI Percutaneous coronary intervention

PES Paclitaxel-eluting stents

PREMIER Prospective registry evaluating myocardial infarction events and recovery

PRISON Primary stenting of totally occluded native coronary arteries

QALY Quality adjusted life year

RAVEL Randomised study with the sirolimus-coated Bx velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions

RCA Right coronary artery

RCT Randomised controlled trial

ROC Receiver operator curve

RR Relative risk

RRISC Reduction of restenosis in saphenous vein grafts with Cypher sirolimus-eluting stents

RVD Reference vessel diameter

SCAAR Swedish coronary angiography and angioplasty registry

SCANDSTENT Stenting of coronary arteries in non-stress/benestent disease

SD Standard deviation

SES Sirolimus-eluting stent

SES-SMART Sirolimus-eluting versus uncoated stents for prevention of restenosis in small coronary arteries

SIRIUS Sirolimus-coated stent in treatment of patients with de novo coronary artery lesions trial

STEMI ST elevation myocardial infarction

ST Stent thrombosis

SVG Saphenous vein graft

TAXUS Paclitaxel-eluting stent trials

TIMI Thrombolysis in Myocardial Infarction

TLR Target lesion revascularisation

TVR Target vessel revascularisation

TYPHOON Trial to assess the use of the Cypher stent in acute myocardial infarction treated with angioplasty

WCC World congress of cardiology

1. Introduction

Percutaneous coronary intervention (PCI) to treat coronary artery disease is one of the most commonly performed medical procedures in Europe and North America. Over the last decade in Scotland, the number of PCI procedures has increased more than three-fold with 6,380 procedures performed between April 2007 and March 2008.[1,2] As a method for revascularisation in coronary artery disease, PCI procedures are now almost twice as common as coronary artery bypass grafting (CABG); there has been a plateau in the rates of CABG, and a year-on-year rise in PCI.[1,2]

Early PCI procedures involved balloon angioplasty which failed frequently either due to coronary artery re-narrowing (restenosis) or elastic recoil of the treated artery. Restenosis occurred in up to 60% of cases and necessitated repeat procedures or CABG when symptoms recurred. Acute vessel closure was less common (approximately 5% of cases) but caused myocardial infarction (MI) requiring emergency CABG or even death. Its use was therefore limited.[3] Subsequently, bare-metal stents (BMS) were developed. In conjunction with adjuvant anti-platelet treatments, BMS improved outcomes with a reduction in acute complications such as elastic recoil of the treated artery and acute stent thrombosis.[3] However within-stent restenosis, due to neointimal proliferation, became a new limitation of PCI in up to 40% of patients. This complication resulted in recurrent angina and repeat procedures.

Recent years have seen the introduction of drug-eluting stents (DES) designed to inhibit the process of inflammation and smooth muscle cell proliferation responsible for restenosis.[4,5] DES is a term used to refer to a class of stent that is medicated with anti-proliferative medications such as paclitaxel (Taxus stent, Boston Scientific Corp., Natick, MA, USA) and sirolimus (Cypher stent, Cordis Corp., Miami, FL, USA). Initial randomised controlled trials (RCTs) to determine their effectiveness were very promising, with marked reductions in angiographic restenosis and target lesion revascularisation.[4,5] Initial enthusiasm for DES, seen as a panacea for the problem of

restenosis, contributed to a substantial increase in their use throughout North America and Europe.[6-8]

Not all agreed with their widespread use, however. Despite the apparent reduction in recurrent symptoms and the need for repeat procedures, DES were not beneficial in reducing death, MI, or the need for bypass-grafting at 12 months follow-up.[9,10] Early studies were criticised for the use of angiographic rather than clinical endpoints to power trials. Only narrow patient groups with simple coronary lesions were studied in the initial trials, and long-term outcome or safety data were not available for large numbers of patients.[11] The lack of long term data was compounded by reports of a new complication - late stent thrombosis.[12]

Finally, DES are two to three times more expensive than BMS, so there is a significant increase the procedural cost of PCI. The clinical uptake of DES, alongside the already increasing volume of PCI procedures, has created significant pressure on healthcare budgets in many countries leading to, in some cases, explicit rationing.[13-16]

1.1. Overview of study

At the time this study was conceived (April 2006), most of the published literature on DES pertained to the clinical evaluation of these devices in randomised controlled trials, pooling of data at 12 months in meta-analysis, and evaluations of cost-effectiveness. **Chapter 2** contains a review of the existing literature. Relatively little was known about the actual application of DES in clinical practice both within the UK and internationally in terms of geographical variation, patient selection and adoption of DES technology. There were also troubling gaps in the evidence-base for DES for a large number of patients excluded from original clinical trials and limited follow up beyond 12 months. Finally, “best practice” with respect to stent selection during PCI was poorly defined, as evidenced by the lack of detailed clinical guidance on the use of DES. Instead, guidelines in the UK were primarily designed to limit use on financial grounds. Nonetheless clinicians were already making day-to-day

decisions on selection and deployment of DES with the clear knock-on effects to patients in terms of risk/benefit ratio, and to healthcare provision in terms of budgets and equity of use.

Anecdotal accounts suggested there were geographical variations in practice. Furthermore, within a healthcare system governed by standard guidelines and a uniform payment system it was not known whether practice was consistent. **Chapter 3** of this MD thesis, therefore, aims to detail geographical and operator variations in DES use within Scotland. This section then broadens its scope to compare usage of DES internationally, examining DES adoption and utilisation in Europe and North America. Data included in the analysis overlap with the period of practice that followed the major clinical controversy questioning the safety of DES. Again, anecdotal accounts suggested there had been changes in clinical practice; this section examines in detail the trends over time in four different healthcare settings.

A second area where data were lacking was in relation to deployment of DES in patients excluded from RCTs. Following the publication of extensive re-analyses of the original RCT data and epidemiological studies of "all-comers" (described in detail in **Chapter 2**), it became clear that there was a safety concern when DES were being used "off-label", that is on a group of patients largely excluded from the RCTs that aimed to determine DES efficacy. **Chapter 4** seeks to analyse data for the off-label group employing registry information from Scotland, with follow-up from linked national death and hospital admission datasets.

Bringing together the two themes of practice variation and risk/benefit of DES, **Chapter 5** aims to generate detailed criteria for best practice. The Delphi consensus method is well established in other areas of decision-making in coronary revascularisation, and was employed here to generate detailed criteria for DES use. An expert panel from the United Kingdom was invited to complete a novel questionnaire based on hypothetical clinical indications. Experts were asked to

make decisions based on best available evidence outlined by the comprehensive review of the literature (**Chapter 2**) and their clinical judgement. Once appropriateness scores had been generated, they were compared with actual clinical practice in Scotland. To validate the panel findings, clinical outcomes for patients treated according to the consensus criteria were compared to those who were not.

Chapter 6 summarises and concludes the main findings of the thesis.

Chapter 7 describes the personal insights and skills gained from completing this work. It also lists the presentations at national and international conferences and published papers the research has generated to date. **References** and **appendices** conclude the thesis.

1.2. Aims

- To describe geographical variations in the use of DES both within Scotland and between Scotland and other countries (USA, Canada and Western Europe), and the extent to which this can be explained by case-mix.
- To determine whether DES use in patients treated "off-label" is safe and effective
- To use an expert panel to develop criteria for the appropriate use of DES using Delphi consensus methods
- To determine the extent to which current practice in Scotland meets the appropriateness criteria
- To validate the criteria by analysing clinical outcomes

1.3. Research questions

- What clinical factors influence stent choice within Scotland?
- Does the use of DES vary by hospital and operator within Scotland, beyond the influence of clinical factors?

- Does use of DES vary internationally, and if so, can variations be explained by case-mix?
- Has clinical practice changed since descriptions of late-stent thrombosis, and if so, how?
- Are DES effective and safe in groups not studied within clinical trials?
- What clinical subgroups influence appropriateness ratings by the expert panel?
- If appropriateness criteria were applied, what rates of DES use would be expected?
- To what extent does current practice meet the appropriateness criteria? Is there under or overuse and what clinical subgroups influence appropriate use?
- Among patients considered appropriate for a DES, what clinical outcomes could be expected when DES rather than BMS are used in clinical practice?

2. Review of literature

This literature review was used as a description of the contemporary evidence base as part of the modified Delphi method process (see Chapter 5), when experts were initially polled in September 2007. This review is up to date to this point. Subsequently published papers are discussed at relevant points. Sections 2.4 and 2.5 were not included in the Delphi literature review for panellists, but are included here to provide context.

In 2003 and 2004 pivotal clinical trials demonstrated significant reductions in restenosis with the sirolimus-eluting Cypher stent (Cordis Corp., Miami, FL, USA) and paclitaxel-eluting Taxus stent (Boston Scientific Corp., Natick, MA, USA) compared to BMS in the percutaneous treatment of coronary artery disease.[17,18] Consequently, their use increased exponentially. However, there is no evidence from RCTs that DES reduce the risk of death or MI. In fact, some evidence suggests that use of DES may be associated with late stent thrombosis which, in turn, often results in MI or death.[19-21] The aim of this chapter is to provide a comprehensive review of the DES literature, including clinical and cost effectiveness, the limitations of existing trials and the evidence on late stent thrombosis and DES safety.

2.1. Clinical effectiveness of drug-eluting stents

The main clinical indications for PCI are chronic stable angina, ST-elevation MI, and non-ST elevation acute coronary syndrome. These indications vary in the extent to which DES have been evaluated in RCTs.

2.1.1. Chronic stable angina

Chronic stable angina accounts for 40-50% of PCI, and has been the main focus of DES trials (table 1). The original proof of concept studies, such as RAVEL, and TAXUS I and II, were restricted to patients with single, short lesions in moderate diameter vessels who had a low baseline risk of restenosis.[4,5,22] RAVEL reported an angiographic restenosis rate of 26.6% using bare metal stents (BMS) compared with 0% in the sirolimus-eluting

stent (SES) group (p<0.001).[4] Similarly, in TAXUS II, the results were 20.1% and 5.1% for the bare metal and paclitaxel-eluting stent (PES) respectively (p=0.0004).[22]

In the subsequent pivotal trials the inclusion criteria were broadened to cover a wider range of lesions.[17,18] TAXUS IV enrolled 1,314 patients with a target lesion treatable by a single stent and reported a one-year target lesion revascularisation rate of 4.4% for PES compared with 15.1% for BMS (p<0.001). In a post-hoc sub-group analysis, PES outcomes were superior irrespective of lesion length, reference vessel diameter and target vessel.[17] SIRIUS randomised 1,058 patients with a single native target lesion. Over nine months, target lesion revascularisation was required in 4.1% of SES treated patients, compared with 16.6% of controls (p<0.001). SES outcome was better irrespective of sex, diabetic status, lesion length and the presence of overlapping stents.[18] The DIABETES trial included only diabetic patients and again demonstrated superior results for SES compared to bare metal stenting.[23]

The smaller SES-SMART trial focused on patients with very small diameter arteries (mean 2.2mm) and demonstrated lower target lesion revascularisation following SES (7.0% versus 21.1%, p=0.002).[26] In the SCANDSTENT trial, SES were superior to BMS when used for complex lesions such as bifurcation lesions and ostial disease and PRISON II demonstrated superiority when used in chronic total occlusions.[28,29] The recent RRISC trial randomised patients with saphenous vein graft stenoses showing significantly lower target lesion revascularisation with SES (5.3% vs. 21.6%, p=0.047).[30] Compared with the earlier PES trials, patients recruited to TAXUS V and TAXUS VI were more representative of those in routine clinical practice, with a high prevalence of diabetes, longer stenoses, smaller vessels and up to two coronary stents. Both trials showed PES had lower target lesion revascularisation rates compared with BMS.[31,32]

Table 1. Randomised controlled trials of paclitaxel and sirolimus drug-eluting versus bare-metal stents for stable angina and unstable angina

Study	N	Control BMS	Lesion inclusion criteria	Lesion exclusion criteria
Sirolimus-eluting stents (SES)				
RAVEL[4]	238	Bx Velocity*	Single lesion, native vessel, D 2.5-3.5mm, L <18mm	Multivessel, CTO, LMS, ostial, thrombus, bifurcation
SIRIUS[18]	1,058	Bx Velocity*	Single lesion, native vessel, L 15-30mm	Multivessel, CTO, LMS, ostial, thrombus, bifurcation
E-SIRIUS[24]	352	Bx Velocity*	Single lesion, native vessel, D 2.5-3.0mm, L15-32mm	Multivessel, CTO, LMS, ostial, thrombus, bifurcation
C-SIRIUS[25]	100	Bx Velocity*	Single lesion, native vessel, D: 2.5-3.0mm, L 15-32mm	Multivessel, CTO, LMS, ostial, thrombus, bifurcation
SES-SMART[26]	257	Bx Sonic*	Single lesion, native vessel, D: <2.75mm, L, <33mm	Calcified, thrombus, >1 lesion/artery
Pache et al.[27]	500	BeStent2**	Native vessel	LMS, instent restenosis
DIABETES[23]	160	Bx Velocity*	Single lesion, native vessel	LMS, instent restenosis
SCANDSTENT[28]	332	Bx Velocity*	Native vessel. CTO, bifurcation, ostial or angulated	LMS, thrombus
PRISON II[29]	200	Bx Velocity*	Native vessel, CTO >2 weeks	
RRISC[30]	75	Bx Velocity*	SVG, D: 2.5-4mm	Distal graft anastamotic stenosis, occluded SVG
Polymeric paclitaxel-eluting stent (PES)				
TAXUS I[5]	61	NIR*	Single lesion, native vessel, D 3.0-3.5mm, L <12mm	LMS, >1 stent
TAXUS II[22]	536	NIR*	Single lesion, native vessel, D:3-3.5mm, L: <12mm	LMS, >1 stent
TAXUS IV[17]	1,314	Express*	Single lesion, native vessel, D 2.5-3.75mm, L: 10-28mm	LMS; CTO; ostial; thrombus; bifurcation
TAXUS V[31]	1,156	Express2*	Single lesion, native vessel, D 2.25–4.0mm, L 10-46mm	LMS; CTO; ostial; thrombus; bifurcation
TAXUS VI[32]	446	Express2*	Single lesion, native vessel, D 2.5-3.75mm, L 18-40mm	LMS; CTO; ostial; thrombus; bifurcation

BMS bare metal stent, D diameter, L length, CTO chronic total occlusion, LMS left main stem, SVG saphenous vein graft*second generation, **third generation

In 2004, Babapulle et al. undertook a meta-analysis of 11 randomised trials with one-year follow-up. The pooled results demonstrated significant reductions in target lesion revascularisation for both SES (OR 0.15, 95% CI 0.02-0.46) and PES (OR 0.23, 95% CI 0.10-0.42) compared with BMS.[9] In 2006, Roiron et al. published a meta-analysis of 19 trials with up to one year follow up, demonstrating a significant reduction in the composite end-point of major adverse cardiac events with DES compared to BMS (OR 0.46 95% CI 0.41-0.52). This was exclusively due to a reduction in repeat revascularisation.[10]

In the USA, the Food and Drug Administration (FDA) approved indications for which there was evidence from the pivotal clinical trials. Consequently SES were approved for non-MI patients with symptomatic disease and *de novo* lesions shorter than 30mm in native arteries of between 2.5 and 3.5mm diameter.[33] PES were approved for lesions shorter than 28mm in vessels of between 2.5 and 3.75mm diameter.[34] Patients treated within these criteria are referred to as "on-label". However with respect to chronic stable angina and single vessel PCI, many other lesion sub-sets have been subjected to RCTs with one-year follow up reported. These include many "off-label" patients, though follow-up beyond 12 months is not available in large numbers. In addition, there is a lack of RCT evidence comparing use of DES to BMS in vessels with more than one lesion, lesions requiring more than two stents and multi-vessel disease.

2.1.2. ST-elevation myocardial infarction

PCI is used to achieve reperfusion and improve prognosis in patients presenting with ST-elevation MI. Two published randomised trials have directly compared DES with BMS in the management of this group. The PASSION trial compared the Taxus stent against thick strut Express2 (Boston Scientific Corp.) or thin strut Liberte (Boston Scientific Corp.) BMS. At one year follow-up, there was a statistically non-significant reduction in both major adverse cardiac events (8.8% vs. 12.8%, p=0.12), the primary end-point, and target lesion revascularisation (5.3% vs. 7.8%, p=0.31).[35] The TYPHOON

trial compared the Cypher stent with any commercially available BMS. At one year, 7.3% of the SES group had target vessel failure compared with 14.3% following BMS insertion (p=0.004). The difference in the composite end-point was driven by lower target vessel revascularisation rates in the SES group (5.6% vs. 13.4%, p<0.001).[36] In both studies, no difference in MI and cardiac death were noted; to date one year follow up is available in such patients.

A number of factors could explain why TYPHOON produced a statistically significant result in contrast to PASSION. The studies employed different inclusion criteria with mean reference vessel diameters of 2.84mm and 3.24mm respectively. Target lesion revascularisation in the control groups may have varied due to the choice of BMS control and TYPHOON's use of protocol-mandated angiography.

2.1.3. Non-ST elevation acute coronary syndrome

Most trials assessing DES efficacy have explicitly excluded patients with ST-elevation MI. However, they have varied in the extent to which patients with unstable angina and non-ST elevation MI have been included. For example, C-SIRIUS and E-SIRIUS included patients with severe exertional angina or sub-acute rest pain (Braunwald classes I and II) but excluded those with rest pain within the past 48 hours (Braunwald class III) and therefore all non-ST elevation MI patients.[24,25,37] SIRIUS did include patients with Braunwald class III, however the absolute numbers were small, and troponin measurement and ST segment change were not collected at baseline.[18,38] TAXUS IV included 387 patients with unstable angina and 87 with non-ST elevation MI, but the latter group accounted for only 6.6% of the whole study population.[17,39] Table 2 summarises the inclusion criteria for the pivotal SES and PES trials with respect to non-ST acute coronary syndromes. The BASKET trial recruited an unselected series of 826 consecutive patients admitted to one hospital and therefore included 301 patients with acute coronary syndrome, including an unspecified number with non-ST elevation MI.[40] As yet, none of the RCTs has had sufficient power to undertake subgroup analysis in patients presenting with non-ST elevation MI. This deficit is important since such patients account for an increasing proportion of PCI.

Table 2. Patients included in pivotal randomised drug-eluting stent trials

Study	Drug-eluting stent	n	Stable angina n (%)	Braunwald classification of unstable angina I or II n (%)	Braunwald classification of unstable angina III n (%)	NSTEMI n (%)	STEMI
SIRIUS[18,38]	SES	1058	490 (46.3)	527 (49.8)	26 (2.6)	Unknown*	Excluded
TAXUS IV[39,41]	PES	1314	864 (65.8)	289 (21.9)	161 (12.3)	87 (6.6) †‡	Excluded

*Troponin and ST segment change not collected at baseline
† Not mutually exclusive from unstable angina
‡Classified based on troponin or CK-MB elevation in the absence of ST-elevation

SES sirolimus eluting stent PES paclitaxel eluting stent NSTEMI non-ST elevation myocardial infarction STEMI ST-elevation

2.2. Limitations of drug-eluting stent randomised controlled trials

2.2.1. Use of protocol-mandated angiography

It has been standard practice for DES trials to use protocol-mandated angiography at between 6 and 9 months follow up to identify angiographic restenosis. All of the trials listed in Table 1 used protocol-mandated angiography. Angiographic evidence of restenosis may result in repeat revascularisation among asymptomatic patients who would not otherwise have been investigated and treated. This has been termed the "oculostenotic effect" and may influence trial results in two ways. Firstly, it may affect both treatment arms equally resulting in an artificial inflation of end-points for both BMS and DES. Whilst this will not affect estimates of the relative benefit, the absolute benefit associated with DES use may be exaggerated. This problem can be illustrated by considering the ENDEAVOR II trial (the DES here is Endeavor - a zotarolimus-eluting stent (Medtronic Inc., Minneapolis, MN, USA)). In the 592 patients with angiographic follow-up, there was an absolute difference in target lesion revascularisation of 10.0% in favour of DES (5.8% vs. 15.8%, $p<0.0001$). By contrast, in the 591 patients with clinical follow-up only, the absolute difference was only 4.4% (3.4% vs. 7.8%, $p=0.02$).[42]

Secondly, there may be a systematic difference in the effect on DES and BMS. The decision to use angiography at 6-9 months follow-up is based on the natural history of restenosis following bare-metal stenting. If the use of anti-proliferative agents influences, not only the risk of developing restenosis, but also the rate at which it develops, the timing of angiography will impact on estimates of both the relative and absolute differences in outcome.

2.2.2. Choice of bare metal stent control

Where a RCT involves intervention in the control arm, the choice of the control stent may impact on the results. In general, trials have compared DES with a BMS that is identical in every regard other than drug-elution. For example, in the PES and SES trials, the comparison was with their respective second generation stainless steel BMS platforms (Table 1). This approach provides a fair assessment of the extent to which

the addition of the active coating affects outcome. However, it limits the extent to which historical trial results can be generalised to current clinical practice. Technological advances in BMS design, such as development of thinner struts and use of cobalt chromium alloys, have improved outcomes. Observational studies using registry data suggest that use of third generation stents, such as Vision (Guidant Corp., Indianapolis, Indiana, USA) or Driver (Medtronic, Inc., Minneapolis, MN, USA), in vessels over 3mm diameter produces superior results to earlier BMS, with repeat intervention required in 4-7% of cases.[43,44]

Third generation BMS are now widely used in clinical practice. However, their efficacy relative to DES has been assessed in only four randomised clinical trials. As discussed above, the result of PASSION may partly be explained by the choice of control BMS.[35] Similarly in BASKET, the Vision stent used in the control arm had a six month target vessel revascularisation rate of 7.8% - a lower rate than in the pivotal trials. Although the results demonstrated superiority of DES with regard to major adverse cardiac events (7.2% vs. 12.1%, p=0.02), the magnitude of the difference was lower than in previous studies.[40] Unfortunately these end-points from BASKET are not directly comparable with the 9 or 12 month outcomes reported in RCTs. The PASSION and BASKET trials were also atypical in not mandating follow-up angiography.

Pache et al. conducted the only trial specifically aimed at comparing DES with a thin-strut stainless steel stent: BeStent 2 (Medtronic, Inc., Minneapolis, MN, USA).[27] Overall, SES outcomes were superior to the control stent, with target vessel revascularisation rates of 7.2% and 18.8% respectively at one year (p<0.001). Although not statistically powered for sub-group analysis, the authors reported that there was no difference in DES and BMS outcome for larger (>2.8mm) diameter vessels. BeStent2 is not currently commercially available in the UK or Europe. The ENDEAVOR II trial compared the Endeavor stent with its third generation bare-metal stent platform (Driver, Medtronic) in lesions at moderate baseline risk of restenosis. At two years follow-up, there was a significant reduction in target vessel revascularisation using the DES (5.6% vs. 12.5% p<0.0001).[42]

2.3. Late complications

Stent thrombosis is uncommon, but frequently results in MI or sudden death.[20] Late stent thrombosis as a specific problem of DES has been recognised for several years. In 2004, Virmani et al. published the first case report of fatal late stent thrombosis due to localised hypersensitivity 18 months after SES implantation.[45] Subsequently, the same group published a post-mortem study comparing 23 patients who had died more than 30 days following DES insertion with a control group of patients who had died after a similar interval following BMS insertion.[46] The groups were comparable in terms of demographics and artery of implantation. Late stent thrombosis was observed in 14 patients in the DES group compared with only two patients in the BMS group. The aetiology of late stent thrombosis was thought to be multi-factorial. Delayed arterial healing (re-endothelialisation) was a common factor with variable contributions from stenting technique (e.g. two stent bifurcation techniques), malapposition of the stent and the premature withdrawal of dual anti-platelet therapy.

Numerous recent studies analysing long-term outcome in patients treated with DES have raised important questions on the related issues of late stent thrombosis, overall DES safety and clopidogrel use. In general, studies have either examined extended follow-up of the original DES RCT populations through meta-analyses (i.e. predominantly "on-label" patients), or real world practice using observational registries.

2.3.1. Meta-analyses of late outcome

Risk of late stent thrombosis, MI and mortality have been assessed by a number of meta-analyses (table 2). Three analyses aggregated data at study level, using conference presentations and published data,[47-49] whilst five analyses have pooled data at patient-level from original data-sources.[19,50-53]

Table 3. Meta-analyses of late outcomes in DES versus BMS randomised controlled trials

Author	Data abstraction	DES studied	No of RCTs	Outcomes
Nordmann et al.[49]	Study-level	PES SES	9 PES 8 SES	Death, cardiac death, non-cardiac death
Camenzind et al.[47]	Study-level	PES SES	4 SES 5 PES	Q wave MI or death
Bavry et al.[48]	Study-level	PES SES	5 PES 9 SES	Protocol defined stent thrombosis
Holmes et al.[50]	Patient-level	SES	4 SES	Death, cardiac death, non-cardiac death; protocol defined stent thrombosis
Stone et al.[19]	Patient-level	PES SES	5 PES 4 SES	Death, cardiac death, non-cardiac death; all MI, non Q wave MI, Q wave MI; death or MI, cardiac death or MI, death or Q wave MI; protocol defined stent thrombosis
Kastrati et al.[51]	Patient-level	SES	14 SES	Death; death and MI; MACE; protocol defined stent thrombosis
Spaulding et al.[52]	Patient-level	SES	4 SES	Death, cardiovascular death, non-cardiovascular death; death or Q-wave MI; death or MI
Mauri et al.[53]	Patient-level	SES PES	4 SES 5 PES	Protocol defined stent thrombosis; ARC definite thrombosis, ARC definite or probable, ARC any criterion

DES drug-eluting stent PES paclitaxel-eluting stent SES sirolimus-eluting stent RCTs randomised controlled trial MACE major adverse clinical events ARC Academic Research Consortium

Nordmann et al. published a study-level meta-analysis of late mortality in seventeen RCTs.[49] They reported no differences between PES and BMS. Among patients receiving SES, there were no differences in all-cause and cardiac mortality. Non-cardiac death appeared to be more common following SES at two and three years, but not four. Camenzind et al. used a composite end-point of Q-wave MI or death, and demonstrated a higher risk following SES than BMS (6.3% vs. 3.9%, p=0.030).[47] No differences were detected for PES. This study is the only meta-analysis to report an increase in death and MI for DES treated patients.

Bavry et al. examined the risk of angiographically-confirmed stent thrombosis in a study-level meta-analysis of fourteen RCTs.[48] There was no evidence of increased risk following SES. Among those receiving PES, there was an increased risk of late stent thrombosis (>30 days) compared with BMS (0.6% v 0.1%, p=0.034) but no difference in the overall risk of stent thrombosis.

Analysing patient-level data from four SES RCTs, Holmes et al. detected no increased risk of non-cardiac deaths.[50] Holmes' patient-level data and the absence of a consistent pathological basis for excess non-cardiac mortality (excess deaths were due to sepsis, cancer and stroke), suggest that Nordmann's finding may be a statistical anomaly.

Four further patient-level analyses pooled clinical follow-up from the original clinical trials.[19,51-53] Stone et al. showed very late stent thrombosis (after one year) was significantly higher in the PES group.[19] However, the absolute risk was low (0.7% vs. 0.2%, p=0.028) and there were no statistical differences in overall stent thrombosis, MI or mortality. Analysis of SES trials showed similar results, with no difference in mortality or angiographically-proven stent thrombosis overall, but an increase in risk of very late stent thrombosis (0.6% vs. 0%, p=0.025).[19] Analysing the same group of RCTs, Mauri et al. applied new standardised definitions of stent thrombosis (figure 1).[53] No difference in stent thrombosis was observed overall, though in common with other analyses, definite or probable thrombosis occurring after 1 year was higher for both PES and SES. Further meta-analyses of SES trials by Kastratis et al. and Spaulding et al. yielded similar results.[51,52]

One post-hoc analysis of PES RCTs suggested clinically significant end points caused by late stent thrombosis may have been offset by a reduction in complications that result from restenosis and subsequent repeat PCI in BMS.[54] This may explain the discrepancy between the observation of increased late stent thrombosis, and the lack of excess death and MI that would be expected. An alternative explanation would be the limited statistical power of the pooled analyses, due to the low event rate among the less-complex populations studied. For example, more than 10,000 subjects would be required to demonstrate a 1% difference in the absolute rates of death and Q-wave MI as statistically significant.

2.3.2. Observational studies

Of 8,146 unselected patients in the combined Rotterdam and Berne Registries, 2.9% suffered an angiographically-proven stent thrombosis within 44 months of DES insertion.[55] This figure is higher than reports from clinical trials. Stent thromboses occurred up to 35 months after insertion, with late stent thrombosis occurring at a rate of 0.6% per year. No comparative figures were reported for BMS.

Pfisterer et al. followed up the 746 patients in the BASKET-LATE observational study who had not experienced a MACE (death, MI or target vessel revascularisation) by 6 months.[56] Late clinical events, defined as cardiac death and non-fatal MI, were more common following DES than BMS (4.9% vs. 1.3% $p<0.05$) even after adjustment for case-mix (adjusted HR 2.2, 95% CI 1.1-4.7). BASKET-LATE was not powered for relatively uncommon events and applying a narrower definition of late stent thrombosis related events (sudden cardiac death, MI attributable to the target vessel, and angiographically proven stent thrombosis) produced a statistically non-significant numerical increase following DES. Therefore, it is not possible to determine whether the increased risk of clinical end-points can be attributed to an increase in late stent thromboses. When the analyses were applied to the entire BASKET population from baseline, no significant differences were observed because the higher risk of late events for DES was offset by a higher risk of early events (< 30 days) following BMS.

Figure I. Academic Research Consortium definitions of stent thrombosis

Definite stent thrombosis

1. Angiographic confirmation based on TIMI flow and one of the following criteria fulfilled within a 48 hour time window
    1. new acute onset of ischaemic symptoms at rest
    2. new ECG changes suggestive of acute ischaemia
    3. typical rise and fall in cardiac biomarkers as evidence for an acute MI
2. Pathologic confirmation of recent stent thrombosis either at autopsy or via examination of tissue retrieved following thrombectomy

Probable stent thrombosis

1. Any unexplained death within the first 30 days

2. Irrespective of the time after the index procedure, any MI which is related to acute ischaemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible stent thrombosis

Any unexplained death from 30 days following intracoronary stenting until the end of trial follow up

Timing

Early stent thrombosis: 0-30 days post stent implantation

Late stent thrombosis: >30 days to 1 year post stent implantation

Very late stent thrombosis: >1 year post stent implantation

Two Scandinavian national registries have published analyses of "real world" outcome. Lagervist et al. used the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) and showed that, when adjusted for baseline clinical factors, DES use was associated with an increased risk of death or MI beyond 6 months follow-up (adjusted RR 1.20, 95% CI 1.05-1.37).[57] Jensen et al. examined the West Denmark Heart Registry data up to 15 months follow up. Examining the very late events (beyond 12 months), stent thrombosis and MI were more common following DES both before and after adjustments for co-variates. Absolute event rates were low however.[58]

Registry studies provide an important insight but may rely on incomplete data, and are susceptible to residual bias due to unmeasured confounding. In addition, standard statistical methods employed in non-randomised comparisons require a proportional risk of events throughout follow up. Due the non-proportionality of events in both the Swedish and Danish studies, separate estimates for early and late risks are quoted, but overall risk could not be ascertained.

Finally, two registry studies compared outcome following "off-label" and "on-label" DES use. Win et al. demonstrated the rate of stent thrombosis at one year was higher among "off-label" patients than "on-label" patients (1.6% vs 0.9%, adjusted HR 2.29 95% CI 1.02-5.16). Correspondingly, patients treated "off-label" had higher rates of MI (11% vs 5.3%, HR 2.20, 95% CI 1.68-2.89).[59] Beohar et al. also demonstrated an increased risk of stent thrombosis, MI or death (6.9% vs 4.3%, $p<0.001$), though this difference was not statistically significant after adjustment for baseline clinical factors (adjusted HR 1.31, 95% CI 0.99-1.72).[60]

Interpretation of both meta-analysis and observational studies is complicated by the lack of a consistent definition of stent thrombosis. Studies such as BASKET-LATE have employed a wide definition of MI or cardiac death, whilst others, such as the SES trials, have required angiographic confirmation.[18,61] There have also been disparities in the timings applied to stent thromboses. In order to address these inconsistencies, the Academic Research Consortium (a combination of researchers and pharmaceutical

industry representatives) proposed a new definition of definite, probable or possible stent thrombosis, with timing of events classified as early, late or very late (Figure 1).[62]

2.3.3. Role of anti-platelet therapy

In 2004, McFadden et al. reported a case series of four patients with angiographically-confirmed stent thrombosis between 335 and 442 days post DES insertion.[12] The temporal relationship between discontinuation of anti-platelet therapy and late stent thrombosis suggested a causal association. Subsequently, a larger observational study was undertaken using data from the Prospective Registry Evaluating Myocardial Infarction Events and Recovery (PREMIER).[63] Crude all-cause case-fatality at 11 months was significantly higher among the 68 DES patients who discontinued clopidogrel within 30 days, compared with the 432 patients who continued therapy (7.5% vs. 0.7% $p<0.001$). However the characteristics of patients who stopped therapy differed from those who continued it.

In a prospective cohort study Iakovou et al. applied a wider definition of stent thrombosis than previous studies, including sudden cardiac death and post procedural MI.[20] As a result, they reported 1.5% overall stent thrombosis at nine months following DES insertion, compared with 0.4% in the SIRIUS trial. On multivariate analysis, early discontinuation of anti-platelet therapy was the strongest independent predictor of stent thrombosis. Other predictors included renal failure, left ventricular systolic dysfunction and bifurcation lesions which were exclusion criteria in most DES randomised clinical trials. Diabetes was also a significant predictor of late stent thrombosis.

Eisenstein et al. published a retrospective cohort study of 3,609 patients who had received either a BMS or DES and were free of major adverse cardiac events at six months.[64] Patients were classified by whether or not they were still taking clopidogrel and then compared in relation to risk of death or MI up to two years follow up. Among patients with a BMS, clopidogrel had no effect on outcome. Among those with a DES, clopidogrel cessation was associated with a higher risk of death and MI (adjusted OR

1.93 95% CI 1.05-3.56). A separate analysis on patients free from major events at 12 months produced similar results.

It is now widely accepted that discontinuation of anti-platelet therapy increases the risk of late stent thrombosis. However, clopidogrel therapy is associated with increased risk of bleeding and further studies are required to determine the optimal duration of therapy.

2.4. Cost-effectiveness

The unit cost of a DES is 2-3 times that of a BMS with no net survival benefit. Therefore, in economic terms, their increased cost can only be justified on the basis of improved quality of life or reduced post-procedural costs due to fewer repeat revascularisations. The economic studies published to date have produced widely divergent results. Economic analyses performed as part of selective and commercially funded trials suggest that DES are very cost-effective, with the SIRIUS and TAXUS IV trials producing figures of €21,470/QALY and €37,259/QALY respectively.[65,66] However, these figures are at odds with those produced from observational studies and unselected trials.

In Ontario, local registry data were used to determine the risk of repeat revascularisation in 22 sub-groups of patients defined by clinical indication, presence of diabetes, and vessel characteristics. The investigators determined the incremental cost-utility referent to BMS. The lowest cost utility was obtained for diabetic patients, who had lesions longer than 20mm and narrower than 2.75mm, and who had not presented with MI. Even in this group the figure calculated was €149,418/QALY which greatly exceeds the normal cut-off for funding (€45,000/QALY). [67]

The BASKET trial economic analysis was based on an unselected cohort of patients undergoing PCI. The investigators calculated an overall incremental cost/QALY referent to BMS of €73,283/QALY. However, this was based on adverse events over only six months follow-up and did not include the cost of coronary artery bypass grafting.[11] DES were more cost-effective in elderly patients and those with more complex disease, and in patients with a very high baseline risk of restenosis, such as those with very small vessels, there was a net cost-saving.[40]

Even if proven to be cost-effective over a prolonged period of follow-up, the much higher procedural cost associated with DES needs to be taken into account. The early introduction in many countries of strict protocols proscribing DES indications was led largely by economic considerations rather than concerns about clinical effectiveness.

2.5. Implementation – licensing and health-technology assessment

Many countries have produced criteria for the selection of patients for DES. The approaches adopted have varied. In the USA, the Food and Drug Administration (FDA) acts as a licensing body for new drugs and devices. Although no actual restriction is placed on US practitioners by the FDA, the availability of DES for general use was dependent on endorsement from this agency. Therefore, the FDA approved for marketing purposes only those indications for which there was trial evidence of clinical efficacy. Consequently, SES were approved for non-MI patients with symptomatic disease and lesions shorter than 30mm in native arteries of between 2.5 and 3.5mm diameter.[33] PES were approved for lesions shorter than 28mm in vessels of between 2.5 and 3.75mm diameter.[34] Use of DES for patients fulfilling these criteria is referred to as “on-label”.

In 2005, the European Society of Cardiology produced guidelines in which it also recommended that selection for DES should be based on the availability or otherwise of trial evidence. The resultant recommendations were very similar to the FDA licensing, the only difference being to advocate use of PES in lesions up to 40mm length.[68] The 2005 American College of Cardiology advocated use of DES for patients in whom there was trial evidence of benefit and suggested that in patients excluded from trials use of DES should be at the clinician's discretion.[69]

In the UK, a different approach was adopted. In 2003, the National Institute of Clinical Excellence (NICE) issued a health-technology assessment guideline that took account of economic analyses as well as the available trial evidence of clinical effectiveness and observational studies. NICE concluded that DES would only be cost-effective if used in patients with the highest baseline risk of restenosis on the grounds that absolute benefit will be greatest providing that the relative risk reduction is constant in all sub-groups. In doing so, NICE extrapolated the results of trials to patients excluded from them. NICE recommended DES use for patients with lesion length greater than 15mm and in vessels less than 3mm diameter. Diabetes was not a specific indication for DES use, based on multivariate analysis of the TAXUS trial. Patients presenting with MI were not covered by this 2003 guideline.[13] In 2008, the original guideline was reiterated, with DES recommended in the same clinical circumstances. Significantly, these guidelines added a price premium with DES only recommended where the cost was no more than £300 greater than a BMS.

Following an extensive systematic review and economic analysis early policy in Belgium was to only reimburse the full cost of DES to hospitals for use in diabetic patients.[15] A recent health technology assessment (HTA) in Belgium, has concluded against the extension of DES use in other clinical indications on cost grounds.[15] The Canadian province of Ontario, operating within a similarly structured healthcare system to the UK, also produced guidelines that were largely followed by other

Canadian provinces. Based on systematic review and local economic analyses, DES use was recommended in diabetic patients, lesions greater than 18mm, vessels of 2.75mm or less, or an otherwise defined high risk lesion.

2.5.1. Updated guidance following the late stent thrombosis controversy

Following the publication (in abstract form) of studies outlined in section 2.3, the FDA in the USA convened a meeting to address the issue of DES safety. In concluding this 2-day meeting, referring specifically to the stent thrombosis issue the FDA stated

"...the concerns about thrombosis do not outweigh the benefits of DES compared to bare metal stents when DES are implanted within the limits of their approved indications for use."

For "off-label" DES use, the rates of stent thrombosis were felt to be higher than "on-label" use. It was further stated that

"...data on off-label use are limited, and additional studies are needed to determine optimal treatments for more complex patients."

And finally

"...when DES were used off-label, patient outcomes may not be the same as the results observed in the clinical trials conducted to support marketing approval."

The FDA initially recommended clopidogrel therapy for three and six months following SES and PES insertion respectively.[33,34] After an advisory hearing, the FDA suggested 12 months clopidogrel therapy for those patients at low risk of bleeding.[70] In October 2006, the British Cardiovascular Intervention Society reported that the consensus was to maintain clopidogrel therapy for at least one year, and indefinitely in certain patients at higher risk of thrombosis.[71]

2.6. Chapter summary

Early clinical trials of paclitaxel-eluting Taxus stents and sirolimus-eluting Cypher stents demonstrated significant reductions in restenosis - hitherto a frequent complication of PCI. Subsequent meta-analyses confirmed superior outcomes with regard to restenosis and target lesion revascularisation to four years follow up. Whilst a large number of trials have examined DES efficacy in patients presenting with chronic stable angina, some areas of clinical practice have not been subject to the same level of scrutiny. In particular, there is a paucity of trial information on patients presenting with non-ST elevation MI who account for an increasing proportion of patients referred for PCI. Furthermore, inflation of clinical endpoints by protocol-mandated angiography and the technological developments in BMS mean that the results of early randomised trials may over-estimate the clinical effectiveness of DES in contemporary clinical practice.

More recently, the initial enthusiasm to embrace DES technology has been tempered by concerns regarding a possible increase in late stent thrombosis. The absolute increase in late stent thrombosis in randomised populations is very small. Current patient-level analyses pertaining to “on-label” patients do not show that this translates into an increase in the overall risk of stent thrombosis, nor to an increase in MIs or death. Among unselected patients, including those presenting with MI, the risk of stent thrombosis is less well defined and may yet impact markedly on the balance of risk and benefit in patients undergoing PCI. Longer term follow-up is required to determine whether the increased risk of very late stent thrombosis persists or plateaus over time, and to gauge the impact on risk of MI and death.

The role of anti-platelet therapy needs further evaluation. Whilst on anti-platelet therapy, patients are at increased risk of bleeding complications, but early cessation is strongly associated with stent thrombosis. Currently, it is unclear what the ideal duration of therapy is or whether life-long therapy is required.

Despite the plethora of studies on DES, many questions remain unresolved. Clinicians need to balance the risks and benefits for an individual patient. Patients vary in their underlying risk of restenosis, their potential to benefit from DES, their susceptibility to DES complications, and their ability to comply with long-term medication. For many patients, the study evidence needed to finesse the individual decision on use of a DES is still lacking.

3. Drug-eluting stent use in clinical practice

3.1. Variations in clinical practice

Regional variations in healthcare have been long recognised. An account by JA Glover in 1938 of the rates of tonsillectomy among school children in England found a ten-fold difference between regions.[72] In the paper, Glover states that the *"strange facts of incidence* [of tonsillectomy] *speak for themselves",* before surmising that *"one cannot avoid the conclusion that there is a tendency for the operation to be performed as a routine prophylactic ritual for no particular reason and with no particular result"*. There continues to be a wide variation in the incidence of tonsillectomy today.[73] In the United States differences in the rates of common surgical procedures continue to vary widely between regions, though the extent of variation differs by type of surgery.[74,75] Recent examples of variation within the UK healthcare context include studies of prescribing[76] and specialist referral[77] within General Practice.

The existence of wide practice variation in many aspects of medical care could be viewed as contradictory to the goals of evidence-based medicine. If disease can be categorised and the efficacy of treatments assessed using scientific methods, we can determine best practice and this should be employed for all patients. Variation in the treatment should be minimal, and be limited to the relative incidence of disease, patient preference and resource availability.[78] In the UK NHS, resource availability should not cause major variation due to its central funding, and stated goal of equity. And indeed, some would argue that the mere existence of practice variations is *prima facie* evidence of inequalities.[79]

Implicit in the study of practice variations, is the idea that there is a "correct" level of use for a given service, process or treatment and that this "correct" level of usage can be determined through clinical investigation and the application of evidence-based medicine. In resource limited healthcare systems, evidence relates not only to clinical effectiveness but also cost effectiveness.

The existence of significant clinical practice variation implies that certain patients, or defined groups of patients, are either under treated, over treated or both. Under treatment of patients may result in avoidable adverse outcomes. Goodman *et al* examined the relationship between the availability of neonatal intensive care facilities, and neonatal mortality.[80] Variation in the supply of neonatologists and neonatal intensive care beds had been determined in a prior study.[81] National birth and death records were examined, and the neonatal mortality rates within the first 27 days of life calculated. The study adjusted for important clinical determinants of outcome (such as birth weight, maternal age and education). Quintiles in level of resource (neonatologists and neonatal intensive care beds) were determined, and outcomes compared between groups. The authors found that neonatal mortality in the lowest resource quintile was higher than in all four other groups. They also observed that between the 4th quintile and 1st quintile, no further differences in mortality were noted.

Goodman *et al* demonstrated that under resource/under treatment can be shown to be related to poor outcome. Furthermore, in this example, increasing levels of spending and resource beyond a "threshold" did not result in better health outcomes (at least in terms of measurable mortality differences). It could be argued that the spending on expensive care beyond the level that would improve clinical outcomes may be just as damaging. Such over treatment in the UK NHS would result in opportunity costs where other efficacious treatments are forgone. In the US healthcare system, without a central budget, costs have spiraled unsustainably. Overtreatment may also result in iatrogenic disease and unnecessary medicalisation. While practice variation could be regarded as a "symptom", Goodman *et al* aptly illustrate the underlying "disease" and its consequences.

3.1.1 Why does practice vary and relevance to study methods

While practice variation may be undesirable it is often challenging to determine *whether* practice does vary, and if so to then assess the degree of variation and the reasons for it. McPherson outlined the potential reasons for variations in healthcare.[82] These can be summarised as:

1) Omission and inaccuracies from data sources
2) Morbidity and Demography
3) Random variation

Legitimate

4) Availability and supply of resources
5) Clinical judgement
6) Demand from patients

Illegitimate

The above list is divided into "legitimate" and "illegitimate" sources of variation. Legitimate sources of variation do not amount to inequalities, but instead explain why numerical differences in care may occur. If these sources are accounted for the residual variation is likely to be due to other factors that are considered illegitimate, reflecting inequalities.[82]

Central to any study of clinical practice variation is the ability to measure routine care accurately: the extent and quality of the data available will have a significant impact on the quality of the insights that can be obtained. With respect to this study the Scottish Coronary Revascularisation Registry (described in detail in section 3.3.3) was used in comparing Scottish PCI practice. For the study of international variations data came from the following: the Mayo Clinic PCI Registry (Rochester, Minnesota, USA), the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Registry (Alberta, Canada), and the Belgian Working Group on Invasive Cardiology (BWGIC) Registry. These datasets are discussed in more detail in section 3.4.2 and 3.4.5, but they are all of high quality, designed with the aim of comprehensively describing the routine PCI activity for each region. There are low levels of missing data for key variables, and all are centrally collated and validated for completeness and consistency. The comprehensive nature of the data sets used helps to obviate the first of McPherson's sources of variation in this study.

When discussing his potential sources of practice variation, McPherson describes *demographic, morbidity, and random* variation as "legitimate" sources of variation. This makes logical sense given that different populations of age, sex and morbidity

are unlikely to require the same healthcare. The importance of adjusting for morbidity to reduce the level of "legitimate" variation was illustrated in a recent study by Omar *et al*.[76]

Omar *et al* examined prescribing behaviour of General Practitioners (GP) by analyzing variation at patient and local practice level using the UK General Practice Research Database. Previous models of GP prescribing used only demographic profiles to define the indicative prescribing budget for any given practice. Omar *et al* found that only 10% of variation in prescribing could be "explained" by age and sex differences. After adding a validated morbidity score to the model, 80% of the total variation was "explained". The amount of "illegitimate" variation would have been grossly overestimated without the addition of relevant morbidities.

When describing regional variations in practice, it is imperative, therefore, to adjust for differences in clinical factors at the analysis stage. The ability to make this type of adjustment depends on the quality and applicability of the data collected. As described below, the Scottish Revascularisation Registry is an ideal source for performing such analyses. At the planning stage for the international component of this work there was regular liaison with colleagues in the US, Canada and Belgium to ensure comparability between the international data sets for the collected variables.

The final strand of "legitimate" variation is random variation. By using appropriate statistical testing this too can be eliminated.

With comprehensive sources of data and appropriate forms of analysis what remains is the variance due to regional differences in availability and supply of resource (explicit or implicit rationing), clinical judgement and demand from patients. The example below will give a flavour of how these interact.

If two patients with the same condition are treated differently this may be due to differing opinions between clinicians on the optimal treatment. Alternatively, clinicians may agree on optimum treatment but for one patient the hospital

resources (e.g. operating time, competing demands, waiting lists) may prevent it from occurring. Finally, clinicians may agree and local availability may be similar, but these patients are being treated in different countries or regions. Health care policy on the treatment may vary, because of differences in the fundamental objectives of the healthcare system.[79]

From the above example it is clear that there is a hierarchy of variables that could influence clinical practice. Variations in the treatment of individuals may occur, and be influenced by external factors at patient, clinician, hospital, and regional/national levels. The research method that allows variation to be partitioned to levels within a hierarchy is referred to as multilevel analysis.

3.2. Multilevel analysis

Multilevel analysis was initially developed for educational research to address the issue that the performance of individual students within a class was not independent of the performance of others.[83] In assessing, for example, exam performance, factors acting at the level of the class, such as class size, had influence on the whole group of students. Standard statistical methods assume the independence of analysis units (pupils), however, this is not appropriate where a hierarchy (pupils clustered within classes) exists. Indeed, further layers to this hierarchy could be added; for example pupils within classes within schools (a 3-level data structure). Fixed covariate effects may apply at any level of the hierarchy e.g. gender of student (pupil level), size of class (class level) or type of funding for school (school level). Multilevel techniques can be applied to all types of outcome - multilevel linear analysis for a normally distributed outcome, multilevel logistic analysis for a dichotomous outcome and so on.

In multilevel analysis, variance at each defined level (above the lowest level) is estimated. The outcome is not assumed to vary at the lowest level because only one observation is made, exam result per pupil in the above example. In the above 3-level example, the outcome measure (exam result) would be assumed to vary randomly at the level of class and school. The output of a multilevel model

calculates the variance at levels of the hierarchy. In this example for exam results, it would provide an estimate of the between-class variance and between-school variance. Through this procedure, variation in outcome is partitioned within levels of the hierarchy. The "significance" of variance is estimated by comparing the total variance with standard error of variance. If the total variance is greater than twice the standard error, the inclusion of the data hierarchy is considered important to correct estimation.

In common with standard multivariate analysis, estimates are provided for fixed covariate effects. Thus, if class size were the variable of interest it would be entered into the equation in the standard fashion. The output from the model would account for the clustering of pupils within classes, and provide a more "correct" estimate of this fixed effect. Secondly, and importantly for the context of this study, the level of random variation between classes, and the total random variation, may be altered by the addition of the fixed effect. Random variation at class-level may therefore be partially "explained" by the addition of the fixed effect. If the independence of units (pupil exam result) is incorrectly assumed, the variation between classes can be overestimated. Furthermore the standard error, and therefore confidence limits, for the fixed effect (class size) would be too narrow, potentially resulting in a type 1 statistical error.

Multilevel modeling is increasingly employed in cardiovascular research. Examples of its application include analyses of variations in coronary angiography,[84] revascularization,[85] and international outcomes following MI.[86] Furthermore, proof of concept studies from medical literature support hierarchical analysis as valid, useful, and more accurate than "hierarchy naïve" techniques, particularly in the field of practice variations.[87,88]

3.3. Drug-eluting stent use within Scotland – a multilevel analysis of hospital and operator practice

3.3.1. Introduction

DES have been rapidly assimilated into routine cardiology practice for the treatment of coronary heart disease. Compared with conventional BMS, DES reduce restenosis[17,18] - a complication of PCI that increases the risk of recurrent symptoms and repeat procedures. DES do not reduce death or MI and are more expensive than BMS; therefore controversy exists regarding their cost effectiveness.[89,90] In the UK, guidelines were developed at an early stage in the evaluation of DES, with cost effectiveness a significant consideration in the final report.[13,14] DES use was recommended for treating vessels smaller than 3mm or lesions greater than 15mm. However, no study has examined clinical practice within the UK healthcare system, or determined whether practice variation extends to operator level. This is particularly important in light of the significant opportunity costs associated with rapid expansion of an expensive new technology.

As discussed in section 3.1.1, when comparing practice between hospitals, it is imperative to adjust for case-mix differences. Analysis of stent choice during PCI is further complicated by the fact that patients may have more than one lesion treated during a procedure. Some factors, such as age and co-morbidity, are patient characteristics; others, such as angiographic features, act at lesion level. Furthermore, unmeasured factors may influence individual operator practice, independent of case-mix and hospital factors. Conventional multivariate analysis assumes independence of analysis units (in this case lesions), and may thus overestimate variations at higher levels of the hierarchy (in this case patients, operators and hospitals). Multilevel modelling, also known as random effects modelling, incorporates the data hierarchy into the statistical model, allowing a more accurate comparison.[85,86,88] In addition to producing odds ratios for fixed effects, multilevel analysis quantifies the residual, or "unexplained," variation at the different levels of the hierarchy.

3.3.2. Aim

The aim was to determine what clinical factors influenced stent choice within Scotland and whether DES use varied between hospitals and operators within the Scottish NHS beyond the influence of clinical factors.

3.3.3. Methods

3.3.3.1. Data source and study population

Since 1997, the Scottish Coronary Revascularisation Register has routinely collected detailed information prospectively on all PCIs performed in Scottish hospitals. Data are entered by a combination of clinical and administrative staff according to a pre-defined set of standardised data definitions, and centrally collated to form the Scottish register. The database is annually validated for completeness and consistency. Information collected includes demography (including age, gender, and deprivation) co-morbidity (e.g. previous history of MI, stroke, chronic lung disease, diabetes, and hypertension) clinical presentation (e.g. indication for PCI, procedural priority, coronary artery disease severity) and procedural details (type of lesion, length of lesion, diameter of treated vessel, type of stent). In Scotland, relatively few PCIs are performed in the private sector. Therefore, the analysis was restricted to the seven publicly-funded NHS hospitals that performed PCI during the period of study; these were Aberdeen Royal Infirmary, Glasgow Royal Infirmary, Golden Jubilee National Hospital (Clydebank), Hairmyres Hospital (East Kilbride), Royal Infirmary (Edinburgh), Western Infirmary (Glasgow), and Western General Hospital (Edinburgh).

Consecutive patients treated with PCI within these hospitals over a one year period from April 2005 were included in the study. Informed consent to collate and use data is routinely obtained from patients prior to coronary revascularisation and the study was approved by the Scottish Coronary Revascularisation Registry steering Committee and the NHS privacy advisory committee. All patient and operator data were stripped of unique identifiers and, for the purposes of reporting, hospitals are not identified by name.

3.3.3.2. Definitions

Hypertension was a binary variable and defined as blood pressure greater than 140/90mmHg or treatment with antihypertensive therapy. Hyperlipidaemia was defined as total cholesterol concentration greater than 5.2mmol/l or treatment with a lipid-lowering agent. Diabetes was defined as either type I or type II diabetes mellitus. Urgent cases were defined as revascularisation undertaken during the index admission and emergency cases as revascularisation undertaken within 24 hours of admission/referral.

3.3.3.3. Statistical analysis

DES use varied over the 12 month period analysed, therefore quarters of the year was included as a categorical variable to account for changes over time. Hospital was included as a fixed effect, rather than the top level of the hierarchy, for two reasons: with only seven hospitals, there were too few to use hospital as the top level of the hierarchy in a multilevel model;[91] also, one-third of operators practised at more than one hospital, and a multilevel model fully incorporating this cross-classified structure would have been overly complex.

We defined a binary outcome based on DES use in each lesion. If both a DES and BMS were employed in the same lesion, DES use was recorded. Crude proportions of DES use by hospital were compared using a χ^2 test. All patient and lesion covariates listed in Table 1 were tested as univariate for their association with DES use. All factors significantly associated with DES use at the 5% level were included as fixed effects within subsequent multilevel analyses. All variables were treated as categorical, with the exception of age which was continuous. No significant co-linearity was noted.

A multilevel logistic regression model was constructed according to the data hierarchy, with random variation permitted at three-levels: operator, patient and lesion. This three level structure is referred to as the null model, to which hospital, patient and lesion fixed effects were subsequently added. First, hospital was entered as a fixed effect (model 1). Then, patient and lesion fixed co-variate effects (model 2) were assessed. Because more than two-thirds of patients (67.3%) were

treated for single lesions, patient and lesion fixed effects were grouped as "case-mix". Finally, hospital, patient and lesion fixed effects were added within the same model (model 3). All models were adjusted for change over time.

Variance estimates (posterior median (2.5-97.5 percentile range)) for between-operator and between-patient variation for each model are reported. Variance estimates were not produced for the lowest level in the hierarchy (lesion). In the interests of clarity, odds ratios for patient and lesion fixed effects are only shown for model 3 (i.e. the final fully fitted model). Hospital estimates are shown as unadjusted, and for model 3 with p value calculated with a χ^2 test. All multilevel analyses were fitted using Markov Chain Monte Carlo (MCMC) estimation procedure, with a 5,000 iteration "burn-in" phase, and 50,000 iteration chain length. Iteration histories were checked visually to assess mixing. Bayesian deviance information criterion (BDIC) and deviance (MCMC) statistics are shown as indicators of the change in model fit; reductions in these values indicating an improvement.[92] Post-hoc analyses were subsequently performed to further investigate operator-level variation.

The descriptive analyses were performed using SPSS v14.0 software (SPSS Inc, Chicago, Illinois, USA). The multilevel analyses were performed using MLwiN v2.02 (Centre for Multilevel Modelling, University of Bristol, UK).

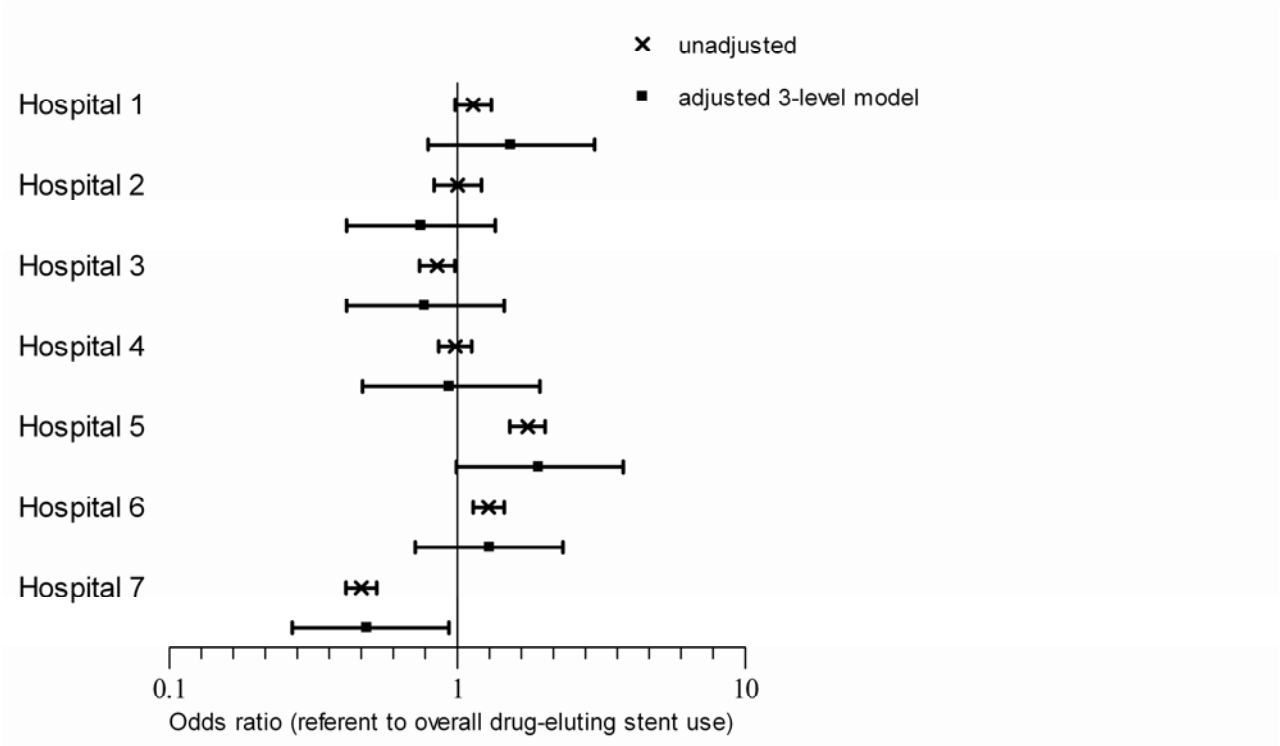
3.3.4. Results

Between April 2005 and March 2006 inclusive, PCI was performed on 8,863 lesions. Two-hundred and eighteen lesions were excluded because no device was recorded, 128 because the procedure was abandoned and 28 because the operator code was missing. The remaining 8,489 lesions equated to 5,967 PCI procedures undertaken by 38 operators in the seven hospitals.

Overall, DES were used in 47.6% of the lesions treated. However, this varied significantly by hospital (Figure 2, χ^2=341.6, p<0.0001) with the crude percentage use ranging from 30.6% to 61.8%. The paclitaxel-eluting Taxus stent (Boston

Figure 2.

Unadjusted hospital estimates and three-level adjusted hospital estimates for drug-eluting stent use



Scientific Corp., Natick, MA, USA) accounted for 80.7% of the DES deployed, and the sirolimus-eluting Cypher stent (Cordis Corp., Miami, FL, USA) for 18.6%.

There were no statistically significant differences between hospitals with regard to sex and diabetic status, but a large number of patient and lesion characteristics were found to vary by hospital of treatment (Table 4). The null 3-level random effects model demonstrated significant variation between operators and between patients (Table 5). Adding the hospital fixed effect reduced operator-level variation by more than 40% (σ^2=0.792 to σ^2=0.445), though patient-level variation increased slightly (model 1, Table 5). When all univariate case-mix predictors of DES use were added, there were only minor alterations in variance estimates (model 2, Table 5), though model fit was improved (indicated by reduced BDIC and deviance statistics for model 2, Table 5). The final model demonstrated variance estimates similar to model 1; significant "unexplained" variation at both operator and patient level remained though further improvements in model fit were noted (model 3, Table 5). Between-hospital variation is represented in Figure 2. Variation persisted even after adjusting for the data hierarchy and case-mix (χ^2=22.1, p=0.001), though as expected the confidence intervals widened.

Table 6 demonstrates the fixed effects estimates for case-mix variables included in model 3 (the final adjusted multilevel analysis). DES use at patient-level was associated with younger, male patients and with more stable presentations of coronary artery disease. However, the most powerful predictors of DES use were lesion factors. Left main coronary artery and left anterior descending artery PCI, the presence of restenosis, longer lesions, smaller vessels, and less tortuous vessels were all associated with an increased probability of DES use. Increased DES use over the 12 months studied is accounted for by the time period variable.

Table 4 Patient and lesion characteristics by hospital

	Hospital 1		Hospital 2		Hospital 3		Hospital 4		Hospital 5		Hospital 6		Hospital 7		P value
PATIENT CHARACTERISTICS	n=780		n=350		n=739		n=861		n=811		n=1,031		n=1,395		
	mean (SD)		**mean (SD)**		**mean (SD)**		**mean (SD)**		**mean (SD)**		**mean (SD)**		**mean (SD)**		
Age	61.9	(12.2)	62.6	(10.2)	59.1	(10.9)	62.2	(11.2)	63.5	(10.5)	61.2	(11.1)	62.2	(10.9)	
	N	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	
Male	548	(70.3)	244	(69.7)	531	(71.8)	584	(67.8)	561	(69.2)	733	(71.1)	1,009	(73.3)	0.34
Diabetes	119	(15.3)	48	(14.1)	105	(14.2)	117	(14.1)	113	(17.9)	161	(15.6)	186	(15.1)	0.47
Previous MI	146	(18.7)	112	(32)	292	(39.5)	334	(38.7)	243	(30.0)	455	(44.1)	401	(28.7)	<0.001
Previous PCI	78	(10.0)	51	(14.6)	86	(11.6)	66	(7.7)	144	(17.8)	132	(12.8)	248	(17.8)	<0.001
Previous CABG	67	(8.6)	19	(5.4)	43	(5.8)	68	(7.9)	94	(11.6)	85	(8.2)	131	(9.4)	0.001
Hyperlipidaemia	497	(63.7)	221	(63.1)	533	(72.1)	488	(56.7)	454	(56.0)	666	(64.6)	1,095	(78.5)	<0.001
Hypertension	408	(52.3)	161	(46.0)	402	(54.4)	355	(41.2)	392	(48.3)	595	(57.7)	632	(45.3)	<0.001
Current smoker	226	(29.0)	115	(33.5)	245	(33.1)	242	(28.7)	245	(38.5)	364	(35.3)	254	(20.9)	<0.001
Vessels treated															<0.001
Single vessel	651	(83.5)	285	(81.4)	607	(82.6)	683	(79.3)	639	(78.8)	809	(78.5)	1,170	(83.9)	
Two vessels	119	(15.3)	60	(17.1)	114	(15.5)	162	(18.8)	162	(20.0)	186	(18.0)	206	(14.8)	
Three vessels	10	(1.3)	5	(1.4)	14	(1.9)	16	(1.9)	10	(1.2)	36	(3.5)	19	(1.4)	
Clinical priority															<0.001
Emergency	74	(9.5)	1	(0.3)	103	(13.9)	91	(10.6)	60	(7.4)	190	(18.4)	200	(14.3)	
Urgent	364	(46.7)	2	(0.6)	257	(34.8)	310	(36.0)	380	(46.9)	360	(34.9)	571	(40.9)	
Elective	342	(43.8)	347	(99.1)	379	(51.3)	460	(53.4)	371	(45.7)	481	(46.7)	624	(44.7)	
Clinical presentation															<0.001
STEMI	56	(7.2)	0	(0)	93	(12.6)	71	(8.2)	57	(7.0)	167	(16.2)	173	(12.4)	
NSTEMI	313	(40.1)	10	(2.9)	208	(28.1)	224	(26.0)	122	(15.0)	309	(30.0)	353	(25.3)	
Unstable Angina	80	(10.3)	12	(3.4)	83	(11.2)	85	(9.9)	198	(24.4)	87	(8.4)	246	(17.6)	
Stable Angina	297	(38.1)	317	(90.6)	341	(46.1)	445	(51.7)	409	(50.4)	443	(43.0)	607	(43.5)	
Other	34	(4.4)	11	(3.1)	14	(1.9)	36	(4.2)	25	(3.1)	25	(2.4)	16	(1.1)	

Table 4 (cont.) Patient and lesion characteristics by hospital

	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6	Hospital 7	P value
LESION CHARACTERISTICS	n=1,017 **n(%)**	n=510 **n(%)**	n=1,028 **n(%)**	n=1,252 **n(%)**	n=1,190 **n(%)**	n=1,608 **n(%)**	n=1,884 **n(%)**	
Treated vessel								<0.001
LMCA	9 (0.9)	2 (0.4)	2 (0.2)	11 (0.9)	24 (2.0)	32 (2.0)	22 (1.2)	
LAD	412 (40.5)	187 (36.7)	381 (37.1)	520 (41.5)	424 (35.7)	620 (38.6)	755 (40.1)	
LCx	230 (22.6)	126 (24.7)	252 (24.5)	276 (22.0)	254 (21.4)	380 (23.6)	404 (21.4)	
RCA	354 (34.8)	188 (36.9)	373 (36.3)	417 (33.3)	434 (36.5)	534 (33.2)	653 (34.7)	
Bypass graft	12 (1.2)	7 (1.4)	20 (1.9)	28 (2.2)	52 (4.4)	42 (2.6)	50 (2.7)	
Lesion length								<0.001
<10mm	306 (30.1)	220 (43.1)	430 (41.8)	441 (35.2)	505 (42.4)	569 (35.4)	833 (44.2)	
10-20mm	518 (50.9)	155 (30.4)	316 (30.7)	427 (34.1)	327 (27.5)	581 (36.1)	717 (38.1)	
>20mm	193 (19.0)	135 (26.5)	282 (27.4)	384 (31.7)	358 (30.1)	458 (28.5)	334 (17.7)	
RVD								<0.001
≤2.5 mm	268 (26.4)	220 (43.1)	430 (41.8)	441 (35.2)	505 (42.4)	569 (35.4)	833 (44.2)	
3mm	417 (41.0)	221 (41.3)	449 (44.1)	424 (33.9)	492 (41.4)	662 (44.2)	697 (37.0)	
≥3.5mm	332 (32.6)	124 (24.3)	322 (31.6)	4.4 (32.3)	341 (28.7)	432 (26.9)	699 (37.1)	
AHA classification								<0.001
A	228 (22.4)	126 (24.7)	360 (35.0)	204 (16.3)	368 (30.9)	235 (14.6)	559 (29.7)	
B1	474 (46.6)	115 (22.5)	169 (16.4)	212 (16.9)	228 (19.1)	431 (26.8)	314 (16.7)	
B2	111 (10.9)	78 (15.3)	193 (18.7)	396 (31.6)	168 (14.1)	358 (22.3)	564 (29.9)	
C	204 (20.1)	191 (37.5)	306 (29.8)	440 (35.1)	426 (35.8)	584 (36.3)	447 (23.7)	
Restenosis	44 (4.3)	17 (3.3)	28 (2.7)	76 (6.1)	47 (3.9)	40 (2.5)	124 (6.6)	<0.001
Thrombus laden	51 (5.0)	5 (1.0)	72 (7.0)	110 (8.8)	66 (5.5)	179 (11.1)	194 (10.3)	<0.001
Bifurcation	68 (6.7)	58 (11.4)	109 (10.6)	270 (21.6)	86 (7.2)	214 (13.3)	242 (12.8)	<0.001
Calcified	34 (3.3)	60 (11.8)	118 (11.5)	159 (12.7)	118 (9.9)	210 (13.1)	312 (16.6)	<0.001
Tortuous	32 (3.1)	46 (9.0)	159 (15.5)	187 (14.9)	176 (14.8)	107 (6.7)	442 (22.4)	<0.001

MI myocardial infarction, PCI percutaneous coronary intervention, CABG coronary artery bypass grafting, CAD coronary artery disease, STEMI ST elevation myocardial infarction, NSTEMI non ST elevation myocardial infarction, LMCA left main coronary artery, LAD left anterior descending, LCx, left circumflex, RCA right coronary artery, RVD reference vessel diameter, AHA American Heart Association.

Table 5. Three-level random effects models for drug-eluting stent use

	Operator-level variance (post. median (2.5-97.5%))	Patient-level variance (post. median (2.5-97.5%))	Deviance (MCMC)	BDIC
Null model[a]	0.792 (0.469-1.414)	3.105 (2.524-3.821)	7775	10116
Model 1[b]	0.445 (0.239-0.861)	3.176 (2.544-3.937)	7743	10102
Model 2[c]	0.827 (0.483-1.483)	2.959 (2.444-3.961)	6639	8592
Model 3[d]	0.486 (0.249-0.971)	3.153 (2.488-3.872)	6584	8569

[a] Adjusted for time period

[b] 3-level random effects model, adjusted for time period and hospital

[c] 3-level random effects model, adjusted for time period, patient and lesion co-variates

[d] 3-level random effects model, adjusted for time period, hospital, patient and lesion co-variates

Table 6. Patient and lesion fixed effects within the final 3-level model

Co-variate effects	OR (95% CI)
Patient-level	
Age (/10 years)	0.72 (0.66-0.78)
Male sex	1.20 (1.01-1.44)
Clinical Presentation	
STEMI	0.30 (0.16-0.55)
NSTEMI	0.59 (0.44-0.81)
Unstable angina	0.81 (0.59-1.14)
Other	0.46 (0.27-0.77)
Clinical Priority	
Emergency	0.99 (0.57-1.73)
Urgent	1.05 (0.78-1.39)
Diabetes	1.39 (1.11-1.76)
Number of vessels treated	
2	1.21 (1.00-1.48)
3	1.38 (0.87-2.21)
Previous PCI	1.16 (0.91-1.51)
Family history of CAD	0.91 (0.76-1.09)
Lesion-level	
Treated vessel	
LMCA	27.52 (13.87-56.83)
LAD	2.39 (1.97-2.90)
LCx	1.06 (0.86-1.31)
Bypass graft	1.07 (0.62-1.84)
Restenosis	8.19 (5.39-12.49)
Lesion length	
10-20mm	2.56 (1.99-3.31)
>20mm	16.35 (10.79-25.43)
RVD	
3mm	0.41 (0.34-0.49)
>3mm	0.13 (0.11-0.17)
AHA classification	
B1	0.65 (0.49-0.87)
B2	0.66 (0.47-0.92)
C	0.61 (0.39-1.11)
Thrombus laden	0.53 (0.38-1.36)
Tortuous	0.72 (0.56-0.92)
Eccentric	1.08 (0.86-1.38)
Time period	
Quarter	
April 2005-June 2005	0.21 (0.16-0.27)
July 2005-Sept 2005	0.40 (0.31-0.50)
Oct 2005-Dec 2005	0.73 (0.59-0.91)

Categorical variables are referent to: female (sex), stable angina (presentation), elective procedure (priority), 1 vessel (vessels treated), RCA (treated vessel), <10mm length (lesion length), ≤2.75mm diameter (vessel diameter), type A (AHA classification) or not present (remainder) STEMI ST elevation myocardial infarction, NSTEMI Non-ST elevation myocardial infarction, PCI percutaneous coronary intervention, CAD coronary artery disease, LMCA left main coronary artery, LAD left anterior descending artery, LCx left circumflex artery, RCA right coronary artery, RVD reference vessel diameter, AHA American Heart Association

To analyse the effect of operator on patient-level variation, a post-hoc 2-level model (patient and lesion) was run without the effect of operator. Between-patient variation increased to σ^2=3.959 (3.202-4.813); an increase of 25%. A further analysis of below and above median operator volume as a fixed effect revealed no association with DES use, and no effect on operator-level variance estimates within the full multilevel hierarchy.

As a supplement to the findings of the multilevel models, DES use for the highest and lowest operator quartiles was compared (Table 7). Within high and low operator use groups, differential DES use by clinical subgroup is evident. Between high and low operator groups, DES use was not statistically different among patients treated for restenosis and left main coronary artery lesions. Marked differences between low and high operator DES use were noted among all other sub-groups, though for lesions at high baseline risk of restenosis (e.g. ≤2.75mm and lesions >20mm length), between group differences were relatively small.

Table 7 Low and high operator drug-eluting stent use, by clinical indication

	Low DES use[a]	High DES use[b]	*p*
	n DES/n category (%)	n DES/n category (%)	
Overall DES use	573/1,972 (27.7)	1451/2,325 (62.4)	<0.001
Diabetes mellitus	86/275 (31.3)	240/328 (69.9)	<0.001
Clinical Presentation			
Stable angina	340/982 (34.6)	784/1190 (65.9)	<0.001
Unstable angina	83/301 (27.6)	241/367 (65.7)	<0.001
NSTEMI	94/486 (19.3)	318/515 (61.7)	<0.001
STEMI	24/166 (14.5)	69/189 (36.5)	<0.001
Treated vessel			
LMCA	14/21 (66.7)	34/45 (75.6)	0.45
LAD	286/768 (37.2)	635/879 (72.2)	<0.001
LCx	112/456 (24.6)	308/521 (59.6)	<0.001
RCA	121/671 (18.0)	449/811 (55.4)	<0.001
Bypass graft	13/56 (23.2)	25/67 (37.5)	<0.001
RVD			
≤2.75	224/459 (48.8)	489/699 (70.0)	<0.001
3mm	242/837 (28.9)	619/913 (67.8)	<0.001
>3mm	80/676 (11.8)	343/711 (48.2)	<0.001
Lesion length			
<10mm	210/959 (21.9)	445/858 (51.9)	<0.001
10-20mm	200/706 (28.3)	407/701 (58.1)	<0.001
>20mm	136/307 (44.3)	599/766 (78.2)	<0.001
Restenosis	90/116 (77.6)	64/86 (74.4)	0.60

All p values calculated using χ^2

[a]nine operators with the lowest DES use

[b]nine operators with the highest DES use

DES drug eluting stent STEMI ST elevation myocardial infarction, NSTEMI Non-ST elevation myocardial infarction, LMCA left main coronary artery, LAD left anterior descending artery, LCx left circumflex artery, RCA right coronary artery, RVD reference vessel diameter

3.3.5. Discussion

Three key features emerge from this analysis. Within the Scottish NHS, a single centrally-funded healthcare system, significant hospital variation in DES use existed even after appropriate multilevel adjustment. Secondly, between-operator practice varied significantly, independent of case-mix, and was the most important determinant of patient-level variation. Operator-level variation was greatly reduced, however, when hospital was introduced as a factor, suggesting local factors heavily influenced operators' practice. Finally, many clinical factors were found to independently influence stent choice; most of these clinical factors are outside of current NICE guidance.

Previous studies from the USA and Italy concluded that differences in the adoption of DES within these healthcare systems were likely to be due to financial considerations, for example, private versus academic and government institutions, and the proportion of patients insured.[6,93] Such distinctions are less relevant within the UK NHS, where all treatments are publicly funded. Furthermore, Scotland has a single national Coronary Heart Disease Advisory Committee and only three regional planning groups responsible for the PCI service. Yet this study demonstrated marked hospital differences in the use of DES even after adjustment for operator practice. However, the variations in hospital practice observed may still be attributable to financial considerations through differential local priority setting, stent availability or integrated care pathways, as well as less tangible influences on group clinical practice.

Significant between-operator variation could exist for a number of reasons. The impact of NICE guidance on some operators is reflected in the higher use of DES in patients, for example, with long coronary stenoses.[13] Clinical practice is more complex, however, and includes many more lesion types and patient groups. The important clinical variables and their relative influence on practice are listed in Table 6. Many patient sub-groups commonly encountered have been studied in only small numbers, or excluded from randomised controlled trials (RCTs). Notable examples include patients treated for non-ST elevation MI and multi-vessel PCI. Interventional

cardiologists may therefore differ in their interpretation of the effectiveness of DES in these patients. Some may choose to extrapolate the results of RCTs on selected patients to groups at high baseline risk of restenosis and therefore infer a higher absolute benefit from DES. Others may restrict DES to patients who would have fulfilled the entry criteria for RCTs, or strictly follow existing guidelines. These difficulties in applying published studies and guidelines to clinical practice are likely to have contributed to the demonstrated operator-variation.

The study period largely predates the clinical controversy surrounding late stent thrombosis with DES.[21,47,55,57] This is a serious but rare complication that does not appear to compromise patient outcomes in those studied in RCTs.[19,51,52] However, late stent thrombosis seems to be more common among patients who were not included in pivotal RCTs.[59,60] For resource limited healthcare systems, this introduces a potential paradox. Treating complex patients at high baseline risk of restenosis may be more cost-effective; however in such patients the RCT evidence of safety is generally weaker. This conflict has further complicated clinical decision-making in individual patients.

3.3.5.1. Strengths and weaknesses of the analysis

The strengths of this analysis include comprehensive case ascertainment and the collection of detailed procedural co-variates key to clinical decision-making through the Scottish Coronary Revascularisation Registry. By employing this database and by using appropriate statistical methods, the likelihood that major sources of "legitimate" variation persist have been greatly reduced. Nonetheless, as with all observational studies, unmeasured or unknown clinical confounders may still play a role.

Though the current study was limited to Scotland, the findings are likely to reflect current practice within the UK NHS. In addition, the principles of operator and hospital variation during the adoption of an expensive new technology have wider relevance to many other countries that have similar financial restrictions to the UK.

Because this was an observational study of actual practice, the case-mix of patients undergoing PCI varied significantly by hospital. Observed case-mix differences are likely to reflect differing baseline patient populations and the selection for investigation and other forms of treatment such as coronary artery bypass grafting, the threshold for which may vary by hospital. An individual operator may also be selected by those referring on the basis of clinical factors (e.g. lesion type) as well as non-clinical characteristics (e.g. threshold for intervention); both are likely to affect the case-mix of individual operators.

The data show that operator volume did not account for the residual operator-level variation demonstrated. However there was very little further data on operator characteristics that may "explain" why individual clinicians' choices vary beyond case-mix differences. This aspect merits further study.

Finally, a large amount of "unexplained" patient-level variation was demonstrated that was largely unaffected by the addition of case-mix co-variates. This variation is entirely attributable to the patients who received multi-lesion PCI (around one-third of the total population). The findings suggest that lesion-level rather patient-level factors determine DES use, with little correlation between the two. Therefore, it is likely that these factors contributed to the large amount of random variation at patient-level.

3.3.6. Conclusion

Variation in DES use was demonstrated at the level of hospital and individual operator. Such variation is unlikely to be explained on demographic or clinical grounds, and could be regarded as "illegitimate" according to Mcpherson's categories indicating genuine inequalities in practice.

Such marked variation is present despite the existence of a recent NICE guideline. The existence of variations *per se* could be regarded as a failure of these guidelines to standardise practice. It could be argued that the existing clinical guidelines do not

reflect the complexities faced in clinical practice, nor are they sufficiently detailed to assist the calculation of risk and benefit for individual patients.

It is unclear whether the inequalities in use of DES reflect under-utilisation by some operators and hospitals or over-utilisation by others; both have important consequences. The variation at operator level (and perhaps some at hospital level due to the “group operator” effect) is likely to reflect uncertainty in the optimum application of DES in clinical practice. Furthermore, these variations are demonstrated in a cohort of patients prior to the major clinical controversy of late stent thrombosis. Uncertainty in stent choice is likely to be increased following this controversy.

3.4. Drug-eluting stent use internationally – variations and time-trends

3.4.1. Introduction

There are no published patient-level analyses comparing international practice in stent choice during PCI. Despite this, variations in DES use between countries are often referred to by authors. Given the issues that underpin practice variation, this is an important empirical gap. Many studies are published analysing outcomes in experimental situations, yet how DES technology is actually applied in reality is of great interest and clear significance to patient care.

Due to the financial consequences of widespread DES use, many healthcare systems have introduced guidelines or encouraged restricted indications for DES use; but such approaches have varied by country.[13-15,94] How these policy decisions, in some cases explicit rationing, have influenced practice differences between countries is unclear. Furthermore, it is also unclear whether, given a financially unrestricted choice, operators would universally implant DES. More broadly, analyses of these issues may provide an insight into the importance of influences at the macro-economic level on the treatment of individuals.

A second area where data are lacking is the impact of several publications doubting the safety of DES (see section 2.3). While the guidelines and policies have mainly assumed DES to be beneficial in all clinical settings and have attempted to limit use on financial grounds to those likely to benefit most, the publication of new data may have affected the clinical risk/benefit at patient level. Again, with only anecdotal accounts available at this point, there are few empirical data to guide debate.

3.4.2. Establishing international contacts and obtaining comparable data extracts

Early in the study I sought international research collaborators with the aim of obtaining parallel PCI data from North America and Europe to allow comparison between differing healthcare systems. Several interventional cardiologists were contacted from the existing research network for the SYNTAX study, of which Dr Oldroyd was a participant.[95] By accessing the network, it was possible to identify

potential international collaborators who had data that fulfilled my criteria for comparison and were able to participate in the study.

Through the network Dr David R Holmes Jr (Mayo Clinic, Rochester, Minnesota) was contacted by telephone. The Mayo Clinic routinely collected information on all PCI from 1976 onwards, including detailed patient, procedural, lesion and stent fields. After considering my study protocol and the details of the data extract requested, the Mayo Clinic PCI registry committee agreed to collaborate and local ethics approval was granted. Direct liaison with the data managers at the Mayo Clinic followed. Separate extracts were received, of anonymised patient, procedure, lesion and stent information from the Mayo Clinic PCI registry going back to the introduction of DES (January 2003). The data coding forms used by the Mayo Clinic were used here to generate the working lesion-level file. The Mayo Clinic's geographical catchment is Olmstead County in Minnesota, although patients from elsewhere are also treated on a private, not for profit, basis. This data provided an indication of practice within the US healthcare system, largely based on a private insurance model.

Contact was also established with Prof Victor Legrand (Liege, Belgium) who leads the Belgian Working Group on Invasive Cardiology (BWGIC). Following a meeting in person at EuroPCR Conference (Barcelona) he provided an extract of data from the Belgian registry. As a comparatively new registry, this provided data from late 2003. In addition, the method of coding these data changed in 2005 to fall in line with the Cardiology Audit and Registration Data Standards (CARDS) - a European Society of Cardiology initiative to standardise data collection and audit.[96] In Belgium, the completion of CARDS audit data was linked to remuneration. As a consequence, data were complete for the variables required by the Belgian Government for payment (such as diabetic status and stent type), but were poorly collected for variables not required (such as lesion details). The Belgian data were therefore of limited completeness. Nonetheless, the data extract provided allowed analysis of stent use in a healthcare system based on compulsory health care insurance and

reimbursement (common in Northern Europe). It was also by far the largest registry, covering a population of 10.4 million people and 32 hospitals.

By using separately established research collaborations, through Prof Pell, contact was made with Dr William A Ghali (Calgary, Canada), lead clinician for the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH). This is a well established dataset[97] used for similar purposes to the Scottish Revascularisation Registry. Following submission of a project proposal and local ethical approval, the APPROACH registry committee agreed to provide access to their data. I liaised with the data manager at APPROACH, who provided a registry extract from January 2003 onwards. The Canadian Healthcare system is similar to that of the UK NHS, with similar regional and country wide cost-conscious guidelines introduced for DES.

All four registries collected detailed patient, procedural and lesion data, however the exact format of the data collected varied considerably between them. Data extracts were reformatted from each country separately using the data codes provided by the respective data managers. Wherever possible the original raw procedural data were used to define key variables with consistent definitions. For example, largest stent diameter was used to define vessel diameter. Logically, using stent data was the most accurate method for reducing the variations introduced by any idiosyncrasies in data recording between registries. After this rigorous process of data formatting, all four registries were combined in a flat lesion file ready for statistical analysis.

3.4.3. Time-trend analysis - rationale

Designing the appropriate analysis for these data was challenging. The aim was to compare countries, with regard to overall adoption, use, and changes in use of DES over time. Simple time trend analysis can chart rolling averages of use over time. This simple type of analysis allows striking graphical presentation, with large volumes of data summarised in an easily understood format.

In common with the analysis of Scottish hospital and operator variation also necessary to adjust for "legitimate" clinical sources of variation between registries, and over time. Finally, the presence of random variations are considered to be classic pitfalls in the analysis of practice variation and needed to be dealt with by appropriate statistical analysis.

Customised graphics software from the statistical package R for Windows[98] was employed to overcome these analytical challenges. This package allowed the DES use estimate to adjust for key clinical variables over time. Such a feature was vital to the elimination of legitimate variation between datasets. I identified important patient subsets *a priori* that would be of interest. The data were stratified by these subsets and presented graphically in a similar fashion.

This statistical package generated "rolling" confidence intervals over time. A logistic regression model was generated for DES use over a defined period, in this case 4 months was chosen as the appropriate time window based on preliminary time trend graphs performed in Excel. The estimate of DES use with 95% confidence interval was calculated for this defined time period. The analysis then shifts the central point of time window forward by one month, recalculating the estimate and confidence interval. This process continues over the whole study period. The graphics package then generated a smoothed "rolling" estimate of DES use, and with it a "rolling" 95% confidence interval. These estimates were graphically presented simultaneously for each registry. Statistically significant differences at any time point, between registries can therefore be assumed where the 95% confidence intervals did not overlap.

Deployment of these statistical methods accomplished several aims: to show variations between countries; to preserve the dimension of time; to allow simple visual inspection of figures to ascertain statistical differences; and to remove demographics and case-mix as sources of variation.

3.4.4. Aims

The aims are to show whether the adoption and use of DES varies internationally and to determine how practice has changed since the stent thrombosis controversy.

3.4.5. Methods

3.4.5.1. Data sources and patient populations

This study involved collaboration between centres from four countries that have established large regional or national PCI datasets of consecutive patients treated in routine clinical practice. The datasets included were the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Registry (Alberta, Canada), Belgian Working Group on Invasive Cardiology (BWGIC) Registry, Mayo Clinic PCI Registry (Rochester, Minnesota, USA), and the Scottish Coronary Revascularisation Registry (Scotland, UK) (table 8). In each registry, data collection and entry is prospective and performed by a combination of administrative and clinical staff. All data were stripped of patient identifiers. Data extracts were obtained from the APPROACH registry, Mayo Clinic PCI registry, and Scottish Revascularisation Registry for all consecutive patients undergoing successful PCI from January 2003 to September 2007 inclusive. Belgian data were available from November 2003 to September 2007. Changes in the collection method for the Belgian registry (introduced in October 2005) resulted in those data only being used for some of the study analyses.

Table 8 Characteristics of registry datasets

Registry	Location	Year established	PCI Centres	Catchment Population	Data collection	DES licensing
APPROACH	Alberta, Canada	1995	3	3.5 million	All patients, prospective	SES: November 2002 PES: September 2003
BWGIC	Belgium	2003	32	10.4 million	All patients, prospective	SES: April 2002 PES: January 2003
Mayo Clinic PCI	Minnesota, USA	1978	1	0.5 million	All patients, prospective	SES: April 2003 PES: March 2004
Scottish Coronary Revascularisation Registry	Scotland, UK	1997	7	5.1 million	All patients, prospective	SES: April 2002 PES: January 2003

APPROACH Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease, BWGIC Belgian Working Group on Invasive Cardiology, PCI Percutaneous Coronary Intervention, DES Drug–eluting stent SES Sirolimus–eluting stent PES Paclitaxel–eluting stent

3.4.5.2. Variables and definitions

Data fields obtained included patient-level demographic details, diabetic status, indication for PCI, and lesion-level angiographic details including type of intervention, type of stent, treated vessel and stent dimensions. Diabetes mellitus was defined as either type I or type II diabetes mellitus treated with insulin or oral hypoglycaemic agents. Clinical presentation was recorded as the principal indication for PCI. Stent diameter was the maximum diameter stent successfully deployed within each lesion, and lesion length was the total length stented. For stratified time trend analyses, stent dimension data were further divided by above and below the median values resulting in four new combined vessel diameter/lesion length categories (≥3mm/<18mm, ≥3mm/≥18mm, <3mm/<18mm <3mm/≥18mm),

3.4.5.3. Statistical analysis

The unit of analysis was the lesion. Lesion, rather than procedure or patient, was chosen as the unit of analysis because more than one type of stent can be used within a procedure creating difficulties in analysis. Second, lesion dimensions play a key role in stent choice in some healthcare settings. The binary outcome for each lesion was defined as treatment with either DES or BMS.

Patients who did not receive a stent were excluded from the analysis. Case mix at baseline was summarized for each registry. Patient and lesion level variables are presented in relation to their respective denominators. Variables are reported as number (percentage) for categorical data, mean (standard deviation) for normally distributed data and median (interquartile range) for skewed data. Data were compared between countries using one-way analysis of variance (normal distribution), Kruskall-Wallis test (skewed or ordinal data) or χ^2 test (categorical data). The date of each procedure was recorded to the level of calendar month. The overall percentage of patients treated with a DES was calculated by country or region over the period of overlap between the US, Canadian and Scottish registries (January 2003-September 2007). Corresponding data from the Belgian registry were

available since November 2003 for overall analysis, and October 2005 for diabetic and clinical indication sub-groups.

To present the data, local likelihood-based non-parametric logistic regression estimates[99] of the trends in percentage DES use were calculated by country and shown graphically with 95% confidence intervals (CIs). The standard deviation of the normal kernel function used was chosen to be 4 months (120 days), based on a visual inspection of figures using a range of alternative parameters. First, an overall unadjusted time trend by country model was constructed. Figures were then produced in a similar fashion for subsets of data: vessel dimensions (≥3mm/<18mm, ≥3mm/≥18mm, <3mm/<18mm <3mm/≥18mm), diabetes, and STEMI. Finally to assess the possible effect of case-mix differences between countries, a generalized additive regression model was used to estimate the time trends in DES use by country. This model was adjusted for age, sex, clinical presentation, diabetic status, vessel diameter and lesion length. Smoothing analyses were performed using the "sm" package (v2.1) within R for Windows v2.7.0.[98] and the adjusted model constructed using the "mgcv" package (v1.3-30), with the non-linear time trend modelled using cubic splines.

3.4.6. Results

3.4.6.1. Baseline characteristics

All consecutive lesions treated with a stent during the study period were included in the overall analysis. In total 178,504 stented lesions in the four geographical areas were included in the overall comparison. For the analyses by diabetic and clinical indication subgroup 118,827 lesions were included from the four registries. For analyses by lesion dimension and the adjusted model 68,781 lesions were included from the APPROACH, Mayo Clinic and Scottish registries. Procedural volume during the study was constant over time within the APPROACH, Mayo Clinic, and BWGIC Registries but was seen to increase year-on-year in the Scottish Registry. Case mix for each registry period is described in table 9. Statistical differences between registries were identified for clinical and demographic case mix variables.

3.4.6.2. Adoption and peak use of drug-eluting stents

The Mayo Clinic PCI Registry demonstrated rapid adoption of DES into clinical practice (figure 3 and 7). Peak use was observed by February 2005, when 91% of stented lesions were treated with a DES. Peak use of greater than 89% was observed in all sub-groups (figures 4-6). In Alberta, the unadjusted estimates demonstrated a more gradual uptake of DES with peak use observed in January 2006 at 56% of lesions (figure 3). In contrast to Alberta, DES uptake in Scotland exhibited a prolonged phase of relatively low utilization prior to a steeper adoption curve during 2005. DES use within Scotland peaked at 58% of lesions in March 2006 (figure 3). At peak use, after adjustment for case mix, there was no statistical difference between the UK and Canadian registries (figure 7). The lowest and latest peak adoption was within Belgium, where DES use peaked at 35% of stented lesions in June 2006 (figure 3).

3.4.6.3. Patient selection for drug-eluting stents

In Alberta and Scotland, selection for DES on patient and lesion characteristics was evident throughout. At peak adoption, high levels of DES use in lesions at highest baseline risk of restenosis (<3mm/≥18mm) was observed: 75% in Alberta, 87% in Scotland and 98% at the Mayo Clinic (figure 4d). However, variation between registries was greater in lesions at moderate risk of restenosis (>3mm/≥18mm, ≤3mm/<18mm (figure 4b and 2c)) and further still for lesions at lowest baseline risk (>3mm/<18mm (figure 4a)) due to lower use in Alberta and Scotland among these subgroups. In Alberta and Scotland, relatively higher DES use by sub-group was also observed for diabetic patients (figure 5). In contrast, lower DES use was observed for STEMI (figure 6) in Scotland and Alberta, but not the Mayo Clinic.

Table 9. Characteristics of patients and lesions within each registry

	APPROACH REGISTRY* (CANADA)	MAYO CLINIC REGISTRY* (USA)	SCOTTISH REGISTRY* (UK)	BWGIC REGISTRY† (BELGIUM)	*p value*
Patients	19,515	6,955	23,507	43,759	
Age (mean±SD)	62.7 (11.7)	66.5 (12.3)	61.6 (10.9)	67.3 (12.5)	<0.001
Male	14,942 (76.4)	4,903 (70.5)	16,630 (70.7)	31,682 (72.4)	<0.001
Diabetes mellitus	4,405 (23.1)	1,712 (24.8)	3,100 (14.1)	8,621 (19.7)	<0.001
Indication for PCI					<0.001
Stable or unstable angina	8,574 (45.7)	3582 (66.4)	15,444 (67.7)	29,669 (67.8)	
NSTEMI	3,849 (20.5)	679 (12.6)	4,838 (21.2)	4,901 (11.2)	
STEMI	6,322 (33.7)	1,131 (21.0)	2,535 (11.1)	9,146 (20.9)	
Number of vessels treated/procedure					<0.001
Single vessel	17845 (87.0)	6013 (86.5)	18877 (83.0)	40,433 (92.4)	
Two vessels	2318 (11.4)	861 (12.4)	3543 (15.6)	3,150 (7.2)	
Three vessels	171 (0.8)	81 (1.1)	317 (1.4)	176 (0.4)	
Lesions					
Total	27,732	9,266	31,783	50,046	
2003	5,076	1,941	5,209	-	
2004	6,153	2,078	6,154	-	
2005	6,445	2,010	7,173	-	
2006	5,867	2,034	7,451	29,069	
2007*	4,191	1,203	5,796	20,977	
Treated vessel					
RCA	10,557 (38.2)	2,949 (31.8)	11,273 (35.5)	-	<0.001
LCx	6,099 (22.1)	2,047 (22.1)	7,060 (22.2)	-	
LAD	10,039 (36.3)	3,417 (36.9)	12,017 (37.8)	-	
LMCA	94 (0.3)	188 (2.0)	436 (1.4)	-	
Bypass graft	538 (1.9)	665 (7.2)	991 (3.1)	-	
Stented length (mm)					
median (IQR)	18 (15-24)	18 (13-23)	18 (15-27)	-	<0.001
<16mm	8,588 (31.2)	3,101 (34.6)	9,215 (29.0)	-	<0.001
16-30mm	14,601 (53.1)	4,629 (51.7)	15,681 (49.3)	-	
≥30mm	4,305 (15.7)	1,223 (13.7)	5,035 (15.8)	-	
Stent diameter (mm)				-	
median (IQR)	3.0 (2.5-3.5)	3.0 (3.0-3.5)	3.0 (2.75-3.5)	-	<0.001
<3 mm	9,651 (35.1)	1,881 (21.0)	8,384 (26.4)	-	<0.001
≥3mm	17,838 (64.9)	7,062 (79.0)	21,568 (67.9)	-	

SD standard deviation IQR inter-quartile range STEMI ST elevation myocardial infarction, NSTEMI Non-ST elevation myocardial infarction, LMCA left main coronary artery, LAD left anterior descending artery, LCx left circumflex artery, RCA right coronary artery

Figure 3 Crude DES use by registry (smooth estimate with 95% confidence interval)

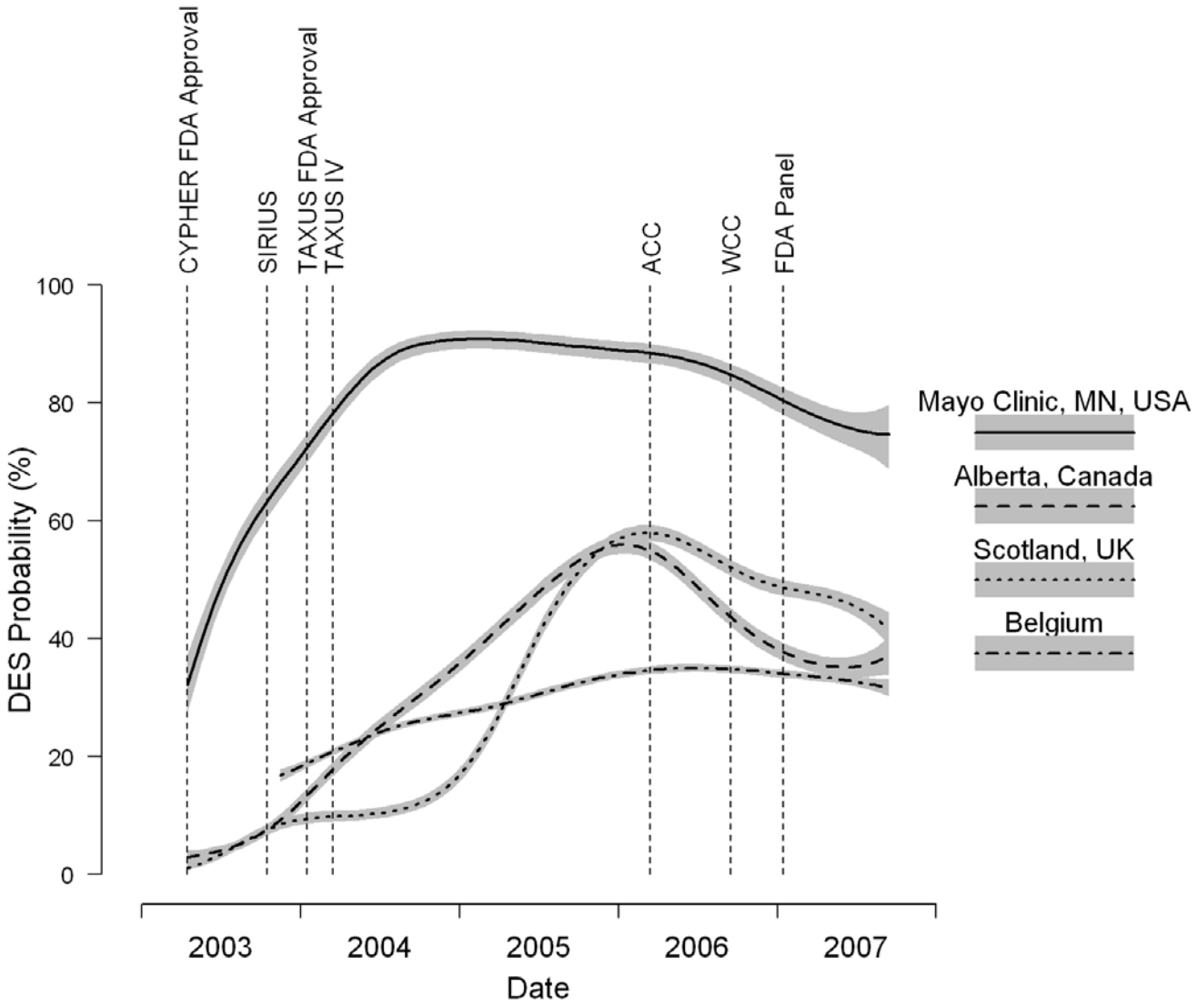


Figure 4

DES use by registry for lesion dimensions, a. ≥3mm, <18mm b. ≥3mm, ≥18mm c. <3mm, <18mm d. <3mm, ≥18mm (smooth estimate with 95% confidence interval)

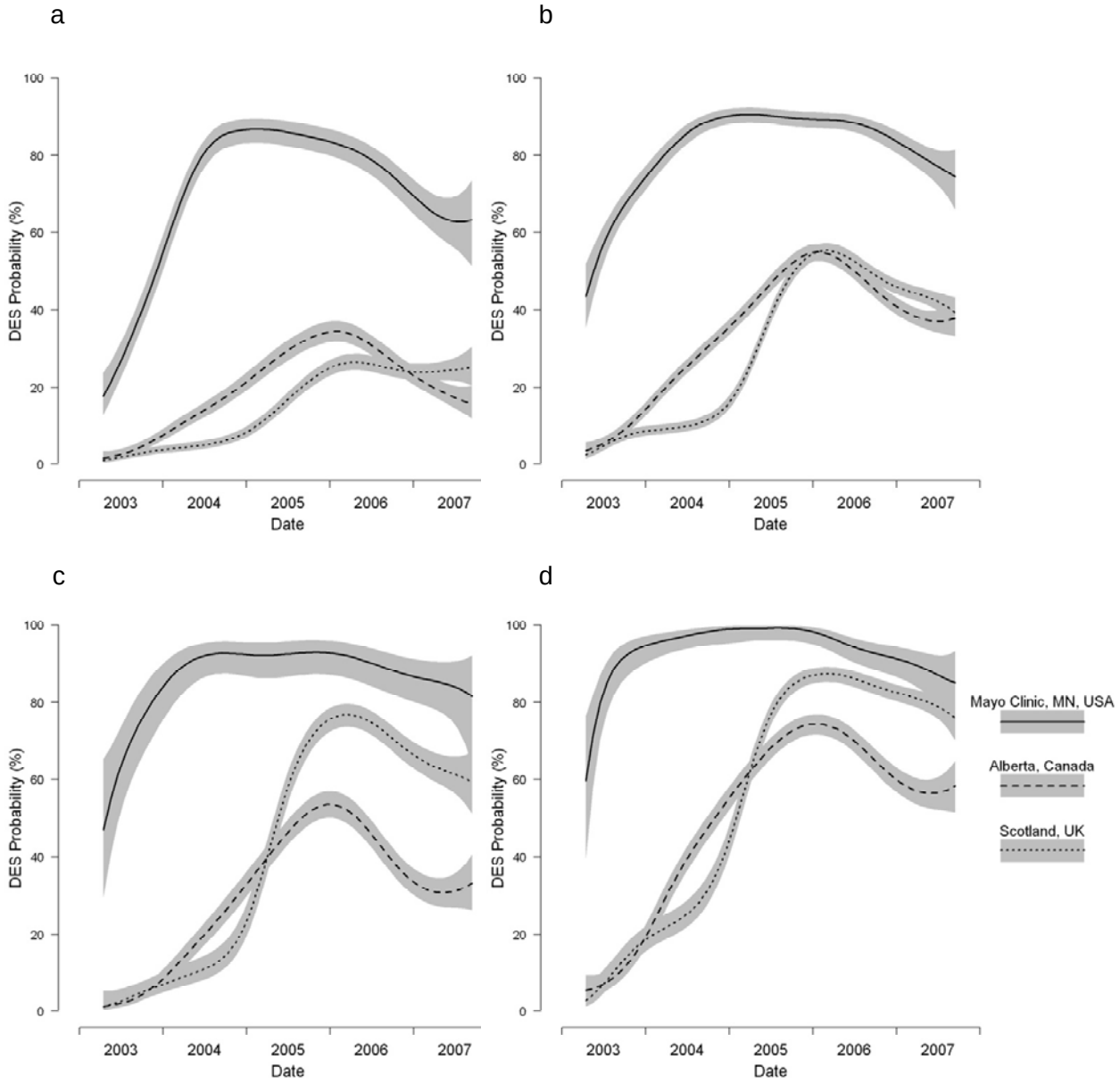


Figure 5

DES use by registry for diabetics (smooth estimate with 95% confidence interval)

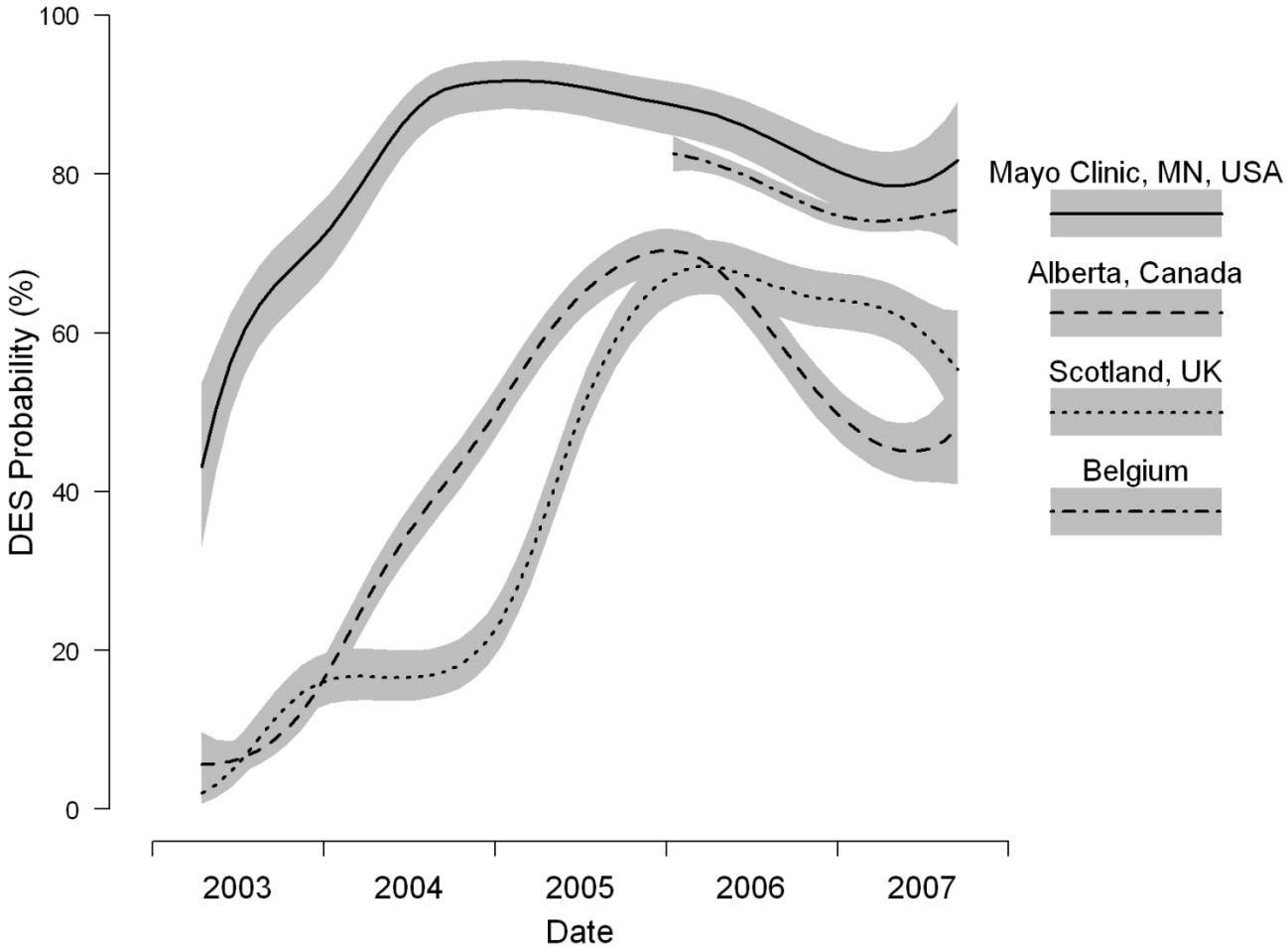


Figure 6

DES use by registry for ST elevation MI (smooth estimate with 95% confidence interval)

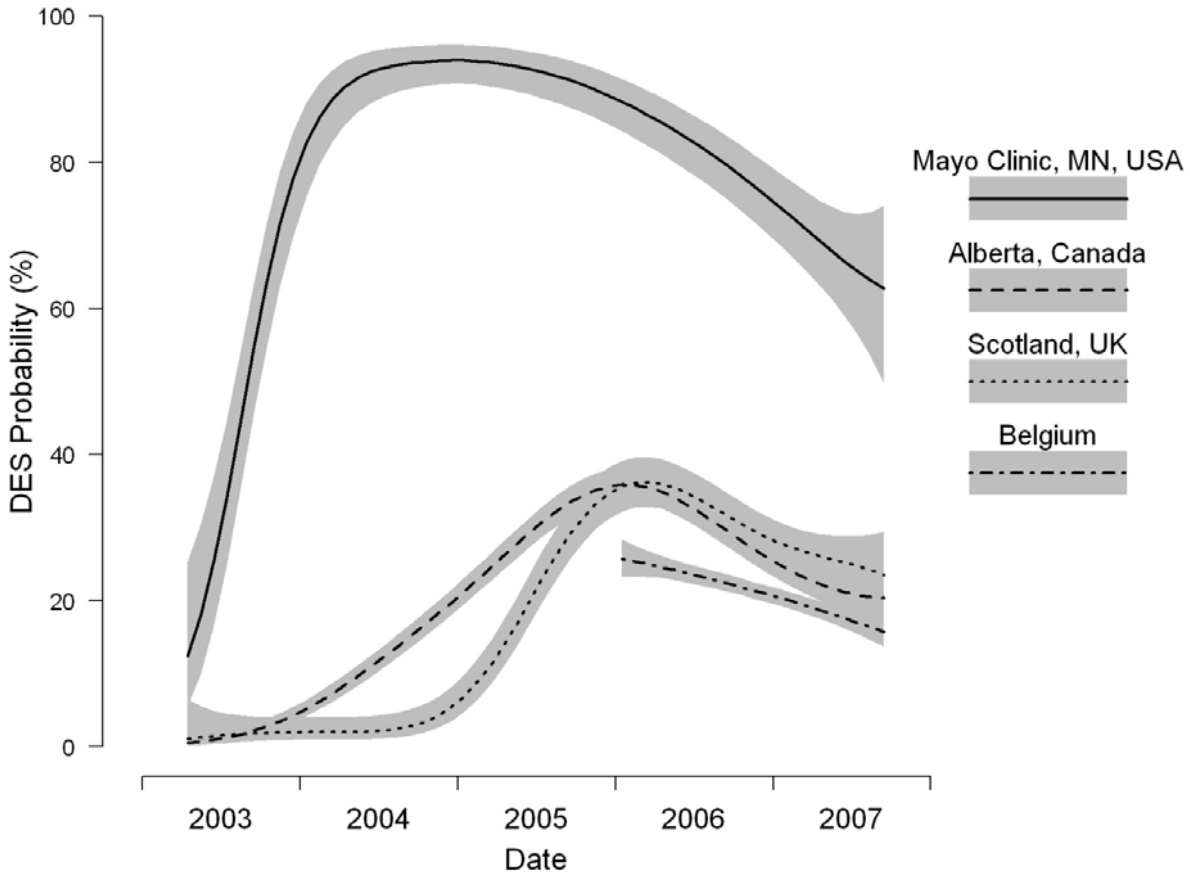
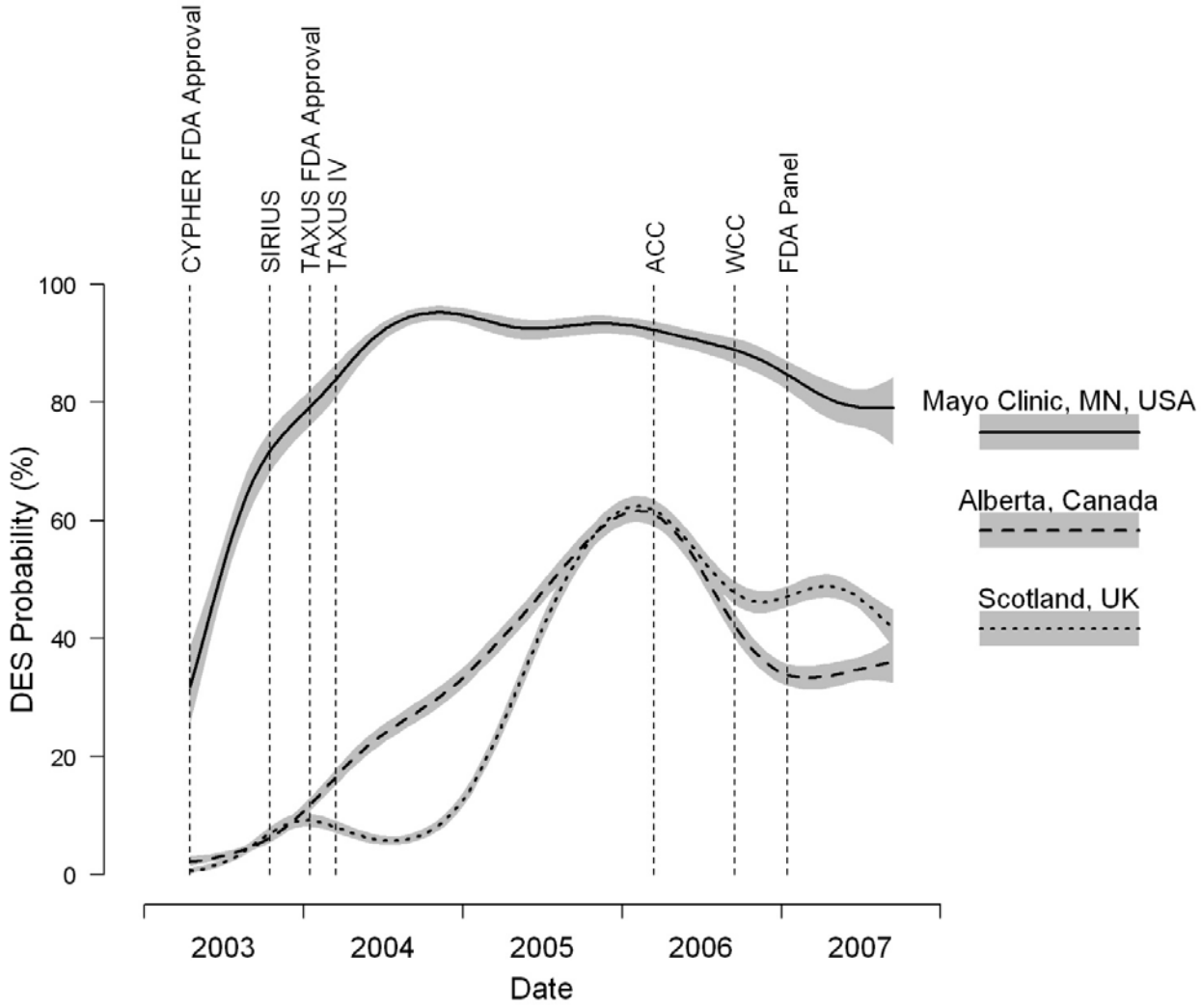


Figure 7

Adjusted DES use by registry (smooth estimate with 95% confidence interval)



Where Belgian sub-group data were available, they demonstrated marked differences in use by diabetic status. DES use among people with diabetes showed no statistical difference to the Mayo Clinic registry in late 2006, and was higher than both the Scottish and Canadian registries (figure 5). In common with the Scottish and Canadian registries, relatively lower DES use was observed for STEMI (figure 6).

3.4.6.4. Reductions in drug-eluting stent use

The Mayo Clinic PCI Registry recorded small reductions in DES use during 2005, followed by a steeper decline during 2006. From the unadjusted smoothed trend line, the estimated absolute reduction from peak DES use was 16%, a relative reduction of 18%. In comparison with the other registries, DES use remained statistically higher throughout maintained above 74% of stented lesions (figure 3 and 7). Differential reductions in DES use by clinical indication were observed in the US registry. Reductions in DES use were greater in patients treated for STEMI (figure 6), and >3mm/<18mm lesions (figure 4a).

In both Alberta and Scotland, DES use started to decline in the second quarter of 2006 (figures 3 and 7). For Alberta, a 19% absolute reduction and 34% relative reduction from peak DES use was observed by the end of the study period. In Scotland, a smaller absolute reduction of 16%, a relative reduction of 28%, was observed. In both registries, pre-evident patient selection remained apparent. In contrast, the BWGIC Registry showed a 1% absolute and 3% relative reduction in DES use during 2006 (figure 3). By the end of the study period, DES were utilized in 75% of stented lesions in the Mayo Clinic, 42% in Scotland, 37% in Alberta and 32% in Belgium (figure 3).

3.4.7. Discussion

This study of PCI practice in four countries demonstrated wide variations in the adoption and utilization of DES. DES use reduced in all registries during 2006 and 2007; the timing and extent of these reductions varied by registry. Marked

differences in utilization by clinical subgroup were evident throughout and observations held even after adjustment for case mix differences.

3.4.7.1. Adoption and peak use

Variations in adoption and peak use exist despite the international nature of clinical scientific evidence and the widespread marketing and availability of DES. In the Mayo Clinic Registry, increased DES use corresponded closely with the FDA approval of the sirolimus-eluting Cypher stent[33] (SES, April 2003) and then paclitaxel-eluting Taxus stent[34] (PES, March 2004) and mirror previous descriptions of US adoption patterns.[6] Both across Europe and in Canada prior licensing of SES (CE Mark April 2002, Health Canada approval November 2002) and PES (CE Mark, January 2003, Health Canada approval September 2003) had occurred. Therefore the delayed adoption of DES outside the US was not related to delayed regulatory approval in these countries.

DES use varies at hospital-level within single healthcare systems (section 3.3)[6,93] Influences are thought to include differences in funding (e.g. private/government, proportion of patients insured), type of hospital (e.g. academic/non academic, urban/rural) and local priority setting. Individual interventional cardiologists also vary in their use of DES (see section 3.3), and their rate of technology adoption.[100] Furthermore it is possible that, in the US in particular, adoption may have been partly driven by concerns of medical malpractice with underuse.[101] However, such disparities in international adoption patterns seem unlikely to be fully explained by individual clinician preference, local hospital factors, differing patient selection for PCI over other treatments (such as CABG or medical therapy) or unaccounted for clinical factors.

Indeed, the adoption of high cost new technologies are thought to be particularly sensitive to the stringency of regulation, the responsiveness of payment systems to changes in practice (e.g. centrally funded, reimbursement, private), the autonomy of local decision making, and overall levels of healthcare funding.[8] This study shows

rapid uptake of DES at the Mayo Clinic - a private, not for profit, academic institution within the influence of the US healthcare system, where stent choice was at the discretion of individual operators. Here there is low regulation, a payment system rapidly responsive to changes in practice, high local autonomy and high levels of healthcare funding. Such an environment encourages rapid and high levels of technology adoption as seen with DES in this study.

As a further illustration, early policy in Belgium was to only reimburse the full cost of DES to hospitals for use in diabetic patients.[15] The influence of this policy on practice is clearly demonstrated in this study. In Belgium, regulation and payment were strictly controlled, local autonomy was therefore low and overall costs controlled; the result was slow adoption and low peak use. A recent health technology assessment (HTA) in Belgium has concluded against the extension of DES use in other clinical indications on cost grounds.[15]

3.4.7.2. Differential selection for drug-eluting stents

Differential selection for DES in Scotland and Alberta is shown here to be on the basis of patient and lesion characteristics. In the UK and Canada early cost-effectiveness analyses and HTAs resulted in clinical policies that favoured the "targeting" of DES to patients felt to be at higher risk of restenosis.[13,16,89,94,102,103] In both the UK and Canada these recommendations explicitly considered cost and were designed to limit overall use. In the UK, The National Institute for Health and Clinical Excellence recommended DES in non-MI patients with lesions greater than 15mm length and in vessels less than 3mm.[13,14] Employing a similar rationale, the Canadian province of Ontario recommended DES use in diabetic patients, in lesions greater than 18mm, vessels of 2.75mm or less, or if there was an otherwise defined high risk lesion.[94]

Both UK and Canadian healthcare systems are largely publicly funded and neither employs a system of direct reimbursement for DES used in recommended indications. In such healthcare systems the interventional cardiologist plays a role in

"gate-keeping", to ensure that overall costs are limited and that DES are used for those considered to have the greatest clinical "need". The data demonstrate that such policy has influenced clinical practice during the period of study.

3.4.7.3. Reductions in drug-eluting stent use

Several studies, initially presented at the WCC conference in September 2006, questioned the safety of DES linked to the risk of late stent thrombosis.[21,47,49,55,57] Subsequent published meta-analyses and large observational studies have shown safety and efficacy of DES without major safety concerns.[19,50-52,104,105] This evidence is particularly strong for "on-label" patients studied in the pivotal randomised controlled trials, though further studies have included other important subgroups.[105-108] It is likely however, that the controversy - and the resultant adverse publicity - has influenced clinical decisions. All registries demonstrated lower DES use during 2007 following a decline in use during 2006. Although the WCC conference in September 2006 is seen as an important landmark, the data presented here suggests that DES use was already declining prior to this time point. Thus the "turn point" for reductions in DES use is perhaps surprising. A possible explanation is that physicians were beginning to manage individual cases of late stent thrombosis in clinical practice, a complication described as far back as 2004.[12,45] Increasing caution in the use of DES, prior to the adverse publicity in September 2006, may have resulted.

By 2007, selection of patients for DES was evident within the US based registry, in particular there was a reduction in use among patients treated for STEMI. In the Canadian and UK based registries, pre-evident factors effecting selection remained, and in common with the Mayo Clinic Registry, reductions in patients treated for STEMI were particularly marked. A possible explanation lies in the importance of dual anti-platelet therapy in preventing thrombotic events;[20,64] an assessment of future patient compliance is particularly challenging within the acute setting and may have discouraged the use of DES.

3.4.7.4. Implications and determinants of utilization

The optimum strategy for adoption and use for DES is not clear. Were DES adopted too early, particularly within US, prior to a full evaluation of the device in many clinical indications? Targeted DES use, for example in the UK and Canada, may make economic sense. However, "off-label" use was encouraged (e.g. very long lesions) and many patients for whom benefit and safety was established, were excluded from guidance. Furthermore, equity of use in systems where the interventional cardiologist acts as "gatekeeper" can be compromised.[109] Finally, a strict reimbursement system, such as in Belgium, appears affective in controlling uptake, limiting overall use and is probably more equitable. However this system may be less flexible to change, unable to respond quickly to the emergence of new data.

Clinically efficacious but expensive new technologies are frequently developed for use in clinical practice. DES are a classic case in point. Wide international differences in the approach to DES have been demonstrated here, as well as varying reductions in use following reports of late stent thrombosis. These findings raise generic questions with respect to the determinants of utilization which include clinical evidence and its applicability to actual practice; public and medical perception, including the importance of marketing and (adverse) publicity; the role of national regulatory and rationing agencies; and the influence and extent of health service control.

3.4.7.5. Strengths and weaknesses of the study

The analysis presented here has provided an overview of international PCI practice since the introduction of DES. While international differences in DES use and recent reductions are often alluded to, no study to date has outlined this in detail. The comparison of North American and European practice is therefore unique. Other strengths include the comprehensive case ascertainment and collection of procedural co-variates key to clinical decision-making. Data collected by the registries are broadly consistent and the majority of relevant clinical details can be

reliably determined. Observations and discussion of practice influences are germane beyond the areas studied.

The study has some weaknesses. As a major academic centre The Mayo Clinic may not necessarily directly reflect US practice; it also treats (hence the database includes) patients from outwith the local region. As a relatively smaller community of operators, practice may also respond more quickly to new information and change practice more synchronously. In addition, a small fraction of total US practice is represented in the data available, with comparatively greater proportions of UK, Canadian (both approximately 10%) and Belgian (close to 100%) clinical activity represented. It is accepted that this is therefore not a comprehensive survey; sample proportions from each country vary and other practice patterns are possible, even within the countries studied.

Registry data were used to represent actual clinical practice, and surrogates such as stent dimensions were relied upon. Furthermore, each dataset is not centrally audited, thus idiosyncrasies between datasets cannot be excluded. Despite this, key variables were defined consistently and were determined from original lesion and patient records.

The study had an observational, time trend design so the results and discussion are necessarily descriptive. To place the findings in context, existing literature was reviewed to identify key external pressures on clinical practice. As with all observational studies I cannot be sure that all relevant variables are accounted for within the adjusted analysis and it is not possible to demonstrate causal link between a given event and change in practice. Segmented time-series analysis can be employed in ecological studies to identify temporal changes in relation to external events; however this approach would have been too simplistic given the complex nature of the trends identified.

As discussed earlier in this section, multilevel analysis would be, in principle, the most appropriate method for analysing international differences in healthcare. It could be argued that several levels exist (country, region/hospital, operator, patient and lesion) within these data, and variations could occur to different degrees within each level. However, the data set out here were not presented in a hierarchical fashion for a number of reasons.

Firstly, only four countries were represented and the minimum required for a multilevel analysis would be twenty.[91] Similarly, within Belgium, 32 hospitals contribute to the dataset (enough to allow within-Belgium hospital variation to be analysed). However, with the Mayo Clinic being a single centre, Alberta three centres and Scotland seven, there would not have been enough to fulfil the multilevel structure. Secondly, other than within Scotland, there was no information on operators.

In the analysis of Scottish practice, patient-level variation was included in the hierarchy. Unfortunately, the datasets proved too large to fit a multilevel model in R. In principle, a multilevel model over time could be produced; however more specialized software would be required and would be a major undertaking. Given the striking differences between countries that were observed with the current models, changing to a multilevel structure was unlikely to substantially alter the overall conclusions.

The potential impact of including multiple lesions per procedure was examined by performing a further exploratory analysis. Using the same adjusted analysis as for figure 7, only one lesion per procedure was selected at random. The two figures (shown in appendix I) compare the analysis containing a single lesion within each procedure (above) and all lesions within each procedure (below). The two figures are virtually indistinguishable. Thus, the potential benefit of altering the analysis to incorporate the hierarchy would not have outweighed the loss in consistency and clarity derived by the current presentation.

3.4.8. Conclusion

International adoption and use of DES showed wide variation in this study of PCI practice in four countries. Reductions in DES use were observed during 2006, but the timing and nature of this reduction also varied geographically.

A consensus did not appear to exist in the optimum application of DES in clinical practice, although influences on stent choice in the "real world" are multi-factorial. These data are a reminder of the gap that often exists between the goal of evidence-base medicine and actual clinical practice.

3.5. Chapter Summary

This chapter has discussed the principles of clinical practice variation and analysed Scottish and International PCI registry data for evidence of such variation in the use of DES. By employing high quality sources of routine data and robust statistical methods the influence of "legitimate" sources of variation was minimised. The remaining practice variation at operator, hospital and international levels was marked. A major source of the variation is likely to be clinical uncertainty. Clinical uncertainty is clearly manifest at operator level but also perhaps in the inconsistent approach by hospitals within Scotland. Furthermore, at country level there are differences in policy on DES use (from no policy through to strict control). These policies are guided by the same clinical evidence, but interpretation within the differing payment structures and healthcare objectives of each country results in wide variations at patient level. Even within the USA where adoption was initially close to universal, reduced DES use and increased patient selection was evident more recently. The reduced use is likely to be as a direct result of the concerning, but poorly defined, risk of late stent thrombosis.

The theme of clinical uncertainty in stent choice will be explored further through the analysis of "off-label" stent use in chapter 4 and the development of comprehensive consensus criteria to define appropriate DES use in chapter 5.

4. "Off-label" drug-eluting stent use

4.1. Introduction

DES were licensed for use in USA and Europe based on evidence of a reduced risk of restenosis and repeat revascularisation obtained from RCTs conducted in selected patients (see section 2.1).[17,18,33,34] The indications for DES use approved by the US Food and Drug Administration (FDA) were derived from the inclusion criteria from the pivotal trials. They comprise a de-novo lesion no longer than 30mm in a native artery with a diameter of 2.5mm to 3.5mm inclusive for the sirolimus-eluting stent, and no longer than 28mm in a native artery with a diameter of 2.5mm to 3.75mm inclusive for the paclitaxel-eluting stent.[33,34] Indications that fulfil the FDA criteria are referred to as "on-label". Pooled analyses have confirmed sustained clinical efficacy and acceptable safety profiles up to four years follow-up among patients with largely "on-label" indications.[19,50-52,104] In clinical practice, DES use during PCI has extended beyond "on-label" indications to include many patients for whom evidence of safety is lacking (see section 3.3 and 3.4). "Off-label" indications include patients with multiple lesions, bypass grafts or bifurcation lesions, and those treated in the context of MI (MI).

Several observational studies of unselected patients have been published; some have raised concerns regarding the safety of DES and, in particular, the risk of late stent thrombosis. Daemens et al. demonstrated a linear increase in stent thrombosis following DES insertion, at a rate of 0.6% per annum between 30 days and 3 years.[55] Both BASKET-LATE and initial findings from the Swedish PCI registry (SCAAR) indicated an increase in MI and death beyond 6 months follow-up when DES were compared with BMS.[21,57] However, an updated analysis of the SCAAR data incorporating more patients and with longer follow-up did not find an increase in death or MI with DES compared to BMS (discussed in section 4.2.1).[110] Jensen et al. demonstrated a small increase in late stent thrombosis among DES treated patients and a corresponding increase in late MI.[58] In contrast, Tu et al demonstrated no difference in MI in an unselected group at two year follow-up, while rate of death at three years was lower for DES treated patients.[105]

Clinical predictors of stent thrombosis following DES include several factors that are considered "off-label".[20,58] This may explain why DES patients treated for "off-label" indications had a higher risk of MI and stent thrombosis compared to those with "on-label" indications.[59,60] However, data comparing DES and BMS specifically in "off-label" indications are limited.

4.2. Observational outcome studies of drug-eluting stents

In observational outcome studies, investigators have no control over treatment assignment and therefore differences in observed covariates between groups can result in biased estimates of treatment effect. Such studies can be criticised for their non-randomised nature and thus a reliance on statistical methods to account for the enduring problems of confounding factors and potential bias. Indeed some have gone so far to say that observational analyses contributed to a misleading picture presented following the World Congress in Cardiology in September 2006.[111] Despite these criticisms, observational studies examining DES and BMS outcomes have accrued in the subsequent period (see table 10).

It is therefore worth considering why this has been the case.

Randomised controlled trials (RCTs) are the gold standard method for establishing the cause-effect relationship of an individual treatment on outcome. However, RCTs are time consuming and costly, and because they are often selective in their recruitment, the potential to generalise from them can be limited. In the case of the DES versus BMS, RCTs were also underpowered to detect differences in hard clinical end points such as MI and death, and they were restricted in their ability to detect differences between sub-groups. Thus when reports of late stent thrombosis came to light, particularly among more complex patients not studied in the pivotal trials,[55,59] the analysis of "real world" outcomes in large numbers of patients became imperative.

Table 10 Observational studies comparing BMS and DES clinical outcomes beyond 1 year

Study	Location	Population	Control group	BMS	DES	Follow-up	Adjustment method	Main treatment difference DES vs BMS
Lagerqvist et al (2007)[57]	Sweden	Unselected patients 2003-4	Contemporary control group	13,738	6,033	3 years	Propensity score regression adjustment and landmark analysis*	Adjusted RR; death 1.18 (1.04-1.35); MI 1.12 (0.95-1.32); Death after 6mo landmark 1.32 (1.11-1.57); MI or death after 6mo landmark 1.20 (1.05-1.37)
Jensen et al (2007)[58]	West Denmark	Unselected patients 2002-5	Contemporary control group	8,847	3,548	15 months	Cox proportional regression and landmark analysis*	Adjusted HRs; Death 0.90 (0.75-1.29); MI 1.14 (0.89-1.45); ST 0.91 (0.67-1.24); Death after 12 months 1.11 (0.62-1.99); MI after 12 moths 4.00 (2.06-7.79); ST 1.78 (0.65-4.91)
Tu et al (2007)[105]	Ontario, Canada	Unselected patients except no left main disease (2003-5)	Contemporary control group	3,751	3751	2 years	Propensity score matching* ¥¥	Absolute rate differences (%); Death -2.2 (p<0.001); MI 0.5 (p=0.95); TVR -3.3 (p<0.001)‡
Marzocchi et al (2007)[112]	Romagna, Italy	Unselected patients except no STEMI (2002-5)	Contemporary control group	7,565	3,064	2 years	Propensity score regression adjustment*	Absolute rate differences (%); Death -0.6 (p=0.35); MI -0.5 (p=0.46); TVR -3.8 (p<0.001); ST 0.4 (p=0.09)‡
Applegate et al (2008)[108]	North Carolina, USA	"Off-label" and "on-label" use 2002-5	Historical cohort (2002-3)	Off-label 854 On-label 281	Off-label 993 On-label 249	2 years	Cox proportional regression*	Adjusted HRs; Death: Off-label 0.72 (0.54-0.94) On-label 0.42 (0.16-1.07); MI or Death: Off-label 0.78 (0.62-0.98) On-label 0.47 (0.23-0.95); TVR Off-label: 0.67 (0.50-0.88) On-label 0.43 (0.23-0.81)
Groeneveld et al (2008)[113]	Pennsylvania, USA	Unselected Medicare (>65) patients 2002-4	Historical control (2002-3)	76,525	76,525	2 years	Propensity score matching¶	Absolute rate differences; Death -2.8% (p<0.001); MI -2% (p<0.001); Revascularisation -1.9% (p<0.001)‡

Mauri et al (2008)[114]	Massachusetts, USA	Acute MI (ST and NSTEMI) 2003-4	Contemporary control group	2,570	2,570	2 years	Propensity score matching*¥	Absolute rate differences (%); Death -2.1 (-3.8 to -0.4); MI -1.4 (-3.0 to 0.2); TVR -4.9% (-6.7 to -1.3)
Shishehbor et al (2008)[115]	Cleveland, USA	Unselected 2003-7	Contemporary control group	1,801	1,801	4 years	Propensity score matching* ¥¥	Absolute rate differences (%); Death -6% (p<0.001)‡
James et al (2009)[110]	Sweden	Unselected 2003-6	Contemporary control group	28,286	19,681	5 years	Propensity score regression adjustment and landmark analysis*	Adjusted RR; Death or MI 0.96 (0.89-1.03); Death or MI before 6mo landmark 0.79 (0.71-0.81) after 6mo landmark 1.11 (1.01-1.23)

HR hazard ratio RR relative risk TVR target vessel revascularisation MI myocardial infarction ST stent thrombosis
*Demographic, clinical and procedural covariates ¶Demographic and basic clinical covariates only ‡no CIs provided ¥ Time variable in PS model to account for adoption of DES ¥¥ No time variable in PS model

Under these conditions, observational analyses using registry data have taken on an important role. Advantages of this approach include the ability to study patients representative of routine clinical practice, in large numbers and in a relatively short timeframe. Therefore studies of sufficient power to detect difference can be quickly available, and the ability to generalise to routine clinical practice becomes possible.

Given the potential pitfalls of observational studies, a critical approach to the methods employed should always be maintained. In particular, PCI registry studies should be scrutinised for the accuracy and relevance of baseline clinical, angiographic and demographic data collected; the type of BMS control group employed; the systems for ascertaining and defining clinical outcomes; the extent of follow-up; and the appropriateness of any statistical methods employed. Table 10 summarises the long term outcome studies comparing DES and BMS.

4.2.1. Drug-eluting stents in Sweden: a case study

The Swedish Coronary Angioplasty and Angiography registry (SCAAR) is a large registry of routine PCI practice in Sweden. It has been used as an audit tool for health service planning and to analyse clinical outcomes. Through use of a 10 digit identifier, patients undergoing PCI can be linked to other databases for death, readmission to hospital, and CABG. The information collected is complete and accurate – greater than 95% correct when validated. Baseline clinical and angiographic details collected are comprehensive. The outcomes are relevant without reporting bias with respect to stent type. Although it contains more patients than the Scottish PCI registry, it is similar in its nature, aims and objectives.[116]

The first Swedish PCI registry study, presented at the WCC in 2006 and then published in NEJM,[57] generated much publicity; colloquially known as the "SCAAR scare".[116] As noted above, the initial results of the SCAAR registry study, including patients treated in 2003 and 2004, showed an increase in late mortality (between 6 months and 4 years) of between 20-30% in patients treated with DES.[57] Subsequent analysis of a patient population from 2003-2006 showed no difference in late

mortality, or other hard clinical endpoints overall. When the authors partitioned the analysis by year of enrolment into the study, adjusted late events were higher in the 2003 cohort but not in the subsequent years.[110] Reflecting on possible reasons for the difference in results from the early cohort (2003) and the later cohorts (2004-6), the authors' cite improved selection for DES over time, increased use of clopidogrel, and better implantation techniques as possible explanations.[116] A further explanation should be considered as likely, however - follow-up bias.

To analyse their data, the SCAAR researchers used a combination of landmark analysis and propensity-score statistical adjustment for differences in baseline clinical variables. Landmark analysis is a form of survival analysis that classifies patients based on an intermediate time point that occurs during follow-up.[117] This method was developed for cancer chemotherapy RCTs to deal with the analytical problem of misclassifying patients who die early in a study as "non-responders", prior to the point where the treatment would have had a biological effect. Also bias would exist, since the longer the patient survived the higher chance of response would be. Thus, the "non-responders" survival would have been artificially lowered and would not provide a fair comparison. To solve this issue, investigators select *a priori* a fixed time point after the initiation of therapy from which to analyse the survival. Clinical events that occur prior to the landmark point discount the patient from entering the analysis. Thus if patients died or went off protocol prior to the landmark, they would not be included.

In SCAAR, the stated aims of using landmark analysis were two-fold. Firstly, the authors considered 6-months to be an appropriate time point to "re-set the clock" for the landmark survival analyses. This corresponded with the recommendation for discontinuing clopidogrel treatment and with the time point where event rates for patients initially treated for MI reduce and become similar to those treated for stable angina.

Secondly, they were able to overcome the problem that the "proportional hazards" assumption was not met in their follow up data. A fundamental requirement of performing Cox-proportional regression analysis is that the event rates in comparator groups remain proportional during follow-up. This assumption can be assessed visually by drawing a Kaplan-Meier curve for the outcomes in question and by statistical testing comparing the event rates over time.[118] Only after this assumption is met can adjustment be made for baseline clinical differences. In the SCAAR registry, the unadjusted Kaplan-Meier survival curves crossed during follow up, clearly indicating non-proportional event rates. By dividing up the data into early and late risks, where the proportionality assumption held, statistical adjustment for differing baseline characteristics could be made. The SCAAR authors used propensity scores to adjust for baseline clinical differences between the groups. Propensity scores will be discussed in detail in the following section (4.3).

By employing this approach, bias may have been introduced into the study design through a combination of factors. First, unequal follow up is evident. By observing the "numbers at risk" column in the SCAAR (2007) study, it can be noted that the number of DES patients at the start of the analysis is 6,035, with BMS 13,735 - a ratio of 1:2.3. By the end of 2.5 years follow up, 606 DES and 3,205 BMS remain within the analysis, - a ratio of 1:5.3.[57] This differential follow up is due to the timing of adoption of DES in Sweden, a fact confirmed in a more recent paper.[116] At the beginning of 2003, the rate of DES use in Sweden was less than 10%. By the end of 2004, the rate of DES use was approximately 50%. Patient selection is likely to have changed over time (see section 3.4), thus the proportions of clinical characteristics present within the survival analysis at, for example, 6 months and 2 years follow up is likely to differ. Statistical adjustment was made on the basis of clinical characteristics of the whole group at the time of PCI, this anomaly cannot be accounted for within the analysis, and its effect on the measured outcomes is difficult to estimate. The issue of differential follow up is compounded by the addition of landmark analysis. By "re-setting the clock" on event rates at 6 months,

but maintaining the statistical adjustment calculated at "day 0", bias introduced by differential follow-up is magnified.

Furthermore, because of particular patterns of DES adoption by clinical sub-group it is likely that landmark analysis introduces further sources of bias. For example, in the datasets analysed in section 3.4 DES use was relatively more common in diabetic patients during adoption (Figure 5), and relatively less common in patients with STEMI (Figure 6). This was true of all of the populations studied in Chapter 3. Diabetic patients have a chronically higher cardiovascular event rate than non-diabetics. Patients following MI have a "window" of increased risk up to 6 months following the index event. This difference in DES use may partially explain the "crossing" of BMS and DES survival curves during follow-up i.e. high early risks with BMS (due to greater use in MI), higher late risks with DES (due to greater use in diabetic patients). By separately analysing early and late events, the SCAAR study may simply reflect this differential pattern of events for diabetic and post MI patients.

It is clearly possible therefore, that the "increase in late events" with DES is due to the presence of relatively more diabetic patients at the end of follow up, unaccounted for statistically, and inflated by the use of landmark analysis to focus on late risks *per se*.

In using registry data where concomitant use of both BMS and DES exists, the pattern of events is likely to be non-proportional, and selection bias at baseline is inevitable. To avoid the problems associated with the SCAAR approach, a different analytic technique is required – propensity-score matching.

4.3. Propensity scores and propensity score matching

Propensity scores were initially described by Rosenbaum and Rubin as *the conditional probability of assignment to a particular treatment given a vector of observed covariates*.[119] Thus for any individual, the propensity score is a

measurement of the likelihood that a patient would have received a treatment on the basis of his or her covariates. Propensity scores are calculated by logistic regression analysis, with the treatment assignment variable as the outcome (in this case BMS=0 and DES=1), and all relevant predictor variables within the model. For every individual patient within the study, a probability (a number between 0 and 1) would be calculated.

Propensity scores are useful because, by definition, individuals with equal (or nearly equal) scores will have the same (or nearly the same) distribution of baseline covariates. Once calculated propensity scores can be used in a number of ways within quasi-experimental studies: regression adjustment, stratification and matching. An example of their use as a regression adjustment is described in 4.2.1[57]; the propensity score model is calculated first, and then adjustment to the survival analysis is made by the addition of the propensity score to the Cox proportional regression model. The effect of adding the propensity score is similar to adding all the co-variates separately. One argument for this two-step propensity score procedure is the ability to generate and test the predictive ability of the model, which can be complex and unlimited by event rate, prior to the assessment of treatment effect.[120]

Stratification is a method commonly used in observational studies to control for baseline differences between control and treatment groups. Subjects are grouped by observed characteristics, and outcomes within strata are compared directly. Stratification as an epidemiological tool is limited when the number of relevant covariates, and therefore the number of required strata, increases. Ultimately, the number of strata required may be large and the number of subjects within each too small to detect differences. Propensity scores can be used to stratify patients into quintiles according to their score. Outcome by strata can be calculated, with >90% of observed bias removed from within each stratum.[119,120]

For this study, propensity score matching was chosen. In common with stratification, matching subjects is limited due to the sheer number of permutations as the number of baseline covariates increases. Because two subjects with similar propensity scores have similar baseline covariates, matching on the basis of the calculated score can allow the "balancing" of covariates within a study. Matching is thought by some authors to be superior to stratification in balancing measured covariates.[121]

Analysis of outcome by propensity score matching is a three stage process: calculation of the propensity score by logistic regression; matching of patients on the basis of the propensity score; and calculation of clinical outcome in the matched groups. At each stage of the process important verifications are required to ensure the study validity, and that common pitfalls have been avoided.

4.3.1. Propensity score calculation

As noted above, multiple logistic regression is used to generate the propensity score. Covariates that are relevant to both treatment assignment and outcome should be included in the baseline model. Mathematical methods can be used to select covariates for a logistic regression model, however here the covariates selected are based on their clinical importance. A "minimum relevant" information set should be used because, theoretically, the addition of too many variables to the model can result in an increase in the variance of the propensity score. This can be problematic at the matching stage, where it may not be possible to match widely dispersed propensity scores, which will result in fewer matched pairs and therefore lower precision in the estimate of treatment effect. In practice, the relevant covariates can be defined a *priori* without much difficulty. The number of covariates within a model is also limited by the number of subjects. However, in this study there were more than enough subjects (>7000) for the number of covariates (approximately 30).

It should be noted that generating estimates of the importance of individual covariates to treatment assignment is not the primary purpose of this stage of the analysis. The key output after fitting the logistic regression model is the individual probability (propensity score) assigned to each subject.

After propensity scores have been generated, the ability of the model to predict treatment assignment can be assessed using the c-statistic. This statistic is generated by plotting the area under the receiver operator curve (ROC) for the propensity score (predicted treatment) against actual treatment assignment. Greater concordance between predicted and actual treatment assignment generates a higher c-statistic. A c-statistic of 0.5 means the model is no better than chance. By convention, a c-statistic of 0.7-0.8 is considered to show good predictive ability and 0.8-0.9 excellent. A further diagnostic test for the baseline model is the Hosmer-Lemeshow goodness-of-fit test. Poorly fitting logistic regression models result in biased estimates of treatment effect.[122]

Finally, the calculated propensity scores can be plotted as histograms for each treatment assignment and compared. For matching to be possible, an area of overlap where the prediction probability range is common to both treatment assignments is necessary. This is termed the common support region and can be assessed visually. Subjects at the extremes of the propensity score, outwith the common support region, can be excluded (a process known as trimming) to ensure comparable groups.[122] The problem of outlying subjects can also be dealt with at the matching stage.

4.3.2. Propensity score matching

Several methods of matching have been proposed. Matching is usually performed by a computer algorithm that obeys pre-specified mathematical rules to ensure close matching of subject in the treatment and control group. Subjects can be matched on a one-to-one or one-to-many basis.

One example of such an algorithm is “5 to 1” matching, where a first attempt is to match the treatment subject propensity score to 5 decimal places with that of the untreated subject. If an exact match is not present, the process tries to match to 4 decimal places. This continues until 1 decimal place. Should this fail, the treatment subject is discarded from the analysis.

A further example is known as nearest neighbour matching, where the treatment subject finds its closest local match (known as greedy heuristic).[105] To prevent an overall illogical match, a “caliper width” can be pre-specified. The caliper width presets the distance (in terms of magnitude of distance between propensity scores) from which the treatment subject can differ from the untreated subject. This ensures a close match between treatment and control. If a treatment subject cannot find a match within the caliper width then the subject is discarded. After matching all treatment subjects within the rules of the matching algorithm, the remaining control subjects are discarded.

After propensity-score matching, there remains a newly formed group of paired subjects (in the case of one-to-one matching).

Assessing the balance of covariates in the matched sample is vital to assess the success of the matching procedure. This should be done by significance testing for all covariates between the treated and untreated subjects.[121] As the dataset is now a matched-pair population the appropriate statistical tests, assuming the non-independence of groups, should be employed. Thus for categorical data the McNemar test should be employed, paired t-tests for continuous data and so on. If matching has been successful, it would be expected that covariates have been “balanced” and that no statistical differences remain between groups.

Standardised differences have also been proposed as a further method for assessing the balance of covariates.[121] The standardised difference is a ratio of the difference of interest to the standard deviation of the observations. This can be calculated for

both categorical and continuous data.[123] Where data are well matched, the standardised difference should be <5%.

Finally, sensitivity analysis can be performed to detect hidden bias. Sensitivity analysis, in general terms, systematically changes the parameters within a model to detect the effects of such changes. The Rosenbaum Bounds approach determines the strength of influence on the treatment outcome of adding an "unobserved" confounding variable to the propensity score match.[119] If a large "unobserved" variable is required to undermine the conclusions regarding treatment effect, the propensity score match is considered to be robust. For the "off-label" use analysis, sensitivity analysis was not performed; however it was introduced in later analysis (see Chapter 5).

4.3.3. Estimating treatment effect

The final stage in propensity score matched outcome studies is to assess the treatment effect by survival analysis. As with randomised controlled trials, the Kaplan-Meier method can be employed to determine survival rates and to graphically represent the pattern of accumulated events. Conventional log-rank testing should not be used, however, because this assumes the independence of samples. To overcome this problem Cox-proportional regression stratified by matched pairs can be used to test statistical significance and generate hazard ratios with confidence intervals.[121]

4.3.4. Advantages of propensity-score matching

A major advantage of matching by propensity scores is the preservation of the pattern of outcome events. In this respect, propensity-score matching can achieve some of the characteristics of a randomised controlled trial. Nonetheless, it should be remembered that while measured differences can be accounted for, hidden or unmeasured factors can be unbalanced between treatment assignment and still result in a biased treatment estimate.

A further advantage is the ability to generate complex models, including interaction terms, to predict treatment assignment. To avoid the issue of follow-up bias, described in section 4.2.1, it was possible to include a time variable within the baseline propensity score model to ensure equal follow up for treated and untreated subjects.

Finally, the explicit removal of known bias can be demonstrated by showing the balance of covariates prior to analysis of outcomes; this process includes the removal of patients outside the common support region or for whom a match cannot be found, who may not have been considered suitable for both treatments. It is worth noting that this kind of exclusion differs from RCT inclusion/exclusion criteria. In the case of DES versus BMS inclusion/exclusion criteria aimed to generate a fair experiment rather than representing all patients that could have either treatment in practice.

4.4. Contemporary versus historical control groups

DES versus BMS outcome studies also vary in the choice of control groups. In general, studies performed in Canada and Europe use contemporary controls,[57,58,105] with studies originating in the US opting for historical controls.[107,108,114,124] The choice of control group is largely "forced" by the trends in adoption in DES described in 3.4.

In one example published in NEJM, Marroquain et al used a historical BMS cohort from 1997-2002, and compared to a DES cohort from 2004-2006.[107] All BMS patients treated from 1997-2002 were included in the control group. As only BMS were available at that time, this group represented 100% of PCI with a stent during that period. Patients treated with BMS from 2004-2006 were excluded from the analysis due to their "highly selected" nature.[107] Thus the DES group included 78% of all PCI with a stent during the 2004-2006 period. As a consequence the DES group were also selected, rather than a genuine "all comers" cohort.[125] Unsurprisingly, marked baseline differences between treatment and control groups resulted from this

recruitment decision. For example, cardiogenic shock, a condition with approximate 50% mortality, was almost three times more common in the BMS group than the DES group (BMS 3.0% vs DES 1.1%, p<0.001) and DES patients were more likely to be diabetic (BMS 27.1% vs DES 35.4%, p<0.001).[107,125]

It is clear that many patients treated with a BMS in the 1997-2002 era (possibly as many as 22%), may not have received a DES in the 2004-2006 era. Thus, a genuine choice between DES and BMS may not have existed for many of these patients. Propensity score matching was not employed in this study, therefore the opportunity to expose (and then exclude) BMS and DES patients' outside of the common support region was missed. It is therefore debatable whether the use of a historical cohort in this study provided a valid comparison of relative treatment effect.

A further disadvantage of employing a control group that pre-dated the DES group by up to nine years was that thin-strut and cobalt chromium BMS were not widely available. This is one example of the many potential changes in practice over time that may render the conclusions out-of-date at best, and biased at worst. One of the key advantages of observational over published randomized design is the comparison with contemporary practice. By using a historical cohort this advantage is lost.

4.5. Aim

The aim here is to analyse medium term clinical outcomes among a cohort of DES patients treated for "off-label" indications, matched to a contemporary BMS control group.

4.6. Methods

4.6.1. Data sources and clinical outcomes

The Scottish Coronary Revascularisation Register has been described in detail in previous sections (see 3.3.2.1 and 3.4.3.1) and was employed again for this analysis.

The Scottish Privacy Advisory Committee approves patient-level linkage to routine databases in order to provide clinical outcomes. Linkage is performed by ISD Scotland by probabilistic matching based on patient identifiers. It is well established and >99% accurate.[126] Ascertainment of outcomes via linkage to Scottish routine databases is also well established and has been shown to be as complete and accurate as prospective follow-up.[127]

The Scottish Morbidity Record collects data on all admissions to Scottish acute hospitals. The principal diagnosis is recorded using the International Classification of Diseases (ICD10) and procedures by the Office for Population, Census and Surveys (OPCS-4) coding system; both are subject to regular quality assurance checks. The General Register Office collates information from all death certificates issued in Scotland, irrespective of whether the person died in the community or in hospital. The cause of death is also coded using the ICD10 classification. Through a separate procedure of internal linkage within the Scottish Coronary Revascularisation Registry it was possible to determine which patients had repeat PCI, and whether this was performed on the target vessel treated in the index procedure.

Thus, through the use of the Scottish Coronary Revascularisation Registry and linked data, three key clinical outcomes were defined: MI (MI), all-cause death and target vessel revascularisation (TVR). MI was defined as admission to hospital with, or death from, MI (ICD10 codes I21 and I22). Target vessel revascularisation was defined as subsequent coronary artery bypass grafting (CABG, OPCS-4 code K40-46) or repeat PCI on a vessel treated during the index procedure. Clinical outcome data were available up to 30th June 2006.

4.6.2. Study population

Patients were considered for inclusion in the study if they underwent a PCI between January 2003 and September 2005 inclusive, during which they had at least one stent inserted for one or more "off-label" indications. In keeping with the exclusion criteria from the pivotal trials[17,18], "off-label" indications were defined as acute MI (non-ST or ST elevation), chronic renal impairment or severe LV dysfunction, stented length greater than 30mm, stent diameter of less than 2.5mm or greater than 3.75mm, PCI of more than one lesion; and intervention to the left main coronary artery, bypass graft, chronic total occlusion, restenosis or bifurcation lesion. Patients were excluded if both BMS and DES were used during the index procedure, or if patients could not be linked to the outcome datasets.

4.6.3. Definitions

Type of DES and BMS were ascertained for descriptive purposes. BMS were characterised as either relatively thick strut (≥0.1mm) stainless steel stents, or as thin strut (<0.1mm) stainless steel or cobalt-chromium stents. Chronic renal impairment was defined as a serum creatinine >200 μmol/L, or renal replacement therapy. Left ventricular dysfunction was defined as mild-moderate (ejection fraction 30-50%) or severe (ejection fraction <30%). Material deprivation was defined by the Carstairs' index of deprivation,[128] calculated by postcode sector according to 2001 census data for social class, overcrowding, car ownership and unemployment.

4.6.4. Statistical analysis

Among the patients who fulfilled "off-label" criteria, the baseline clinical and demographic characteristics varied significantly between DES and BMS treated patients (Table 11). To allow meaningful analysis of clinical outcomes, propensity

scores[119] (conditional probability) for receiving a DES rather than a BMS for each patient were calculated using baseline co-variates within a logistic regression model. A baseline model was defined and included demographic and clinical co-variates selected *a priori* for entry if they were thought to influence both stent choice and outcome (MI, death or TVR). Tables 11 and 12 list the factors that were included in the baseline propensity score model. During the study period, DES were being adopted into clinical practice, therefore a time variable (year of treatment) was entered into the propensity score model to avoid follow-up bias and ensure a comparable control group. Finally, since stent selection may have varied during the adoption of the device, all baseline covariates were allowed to interact with the time variable. Interaction terms were then individually tested within the baseline model and included in the final propensity score model if $p<0.1$. No significant collinearity was noted among co-variates. The c-statistic for the final propensity score model was 0.89 indicating excellent discrimination and the Hosmer-Lemeshow test was non-significant. Patients were then matched using their individual propensity scores on a one-to-one "nearest neighbour" basis. A caliper width of 0.01 was predefined to ensure close matching of DES to BMS controls. Patients in either group who could not be matched on these criteria were not included in the final analysis.

Categorical data were compared using the chi-square test (unmatched) or McNemar test (matched). Continuous data were compared using the 2-sample t-test (unmatched) or paired 2-sample t-test (matched) and expressed as mean (SD). The cumulative probability of outcome-free survival was determined separately for death, MI and TVR for matched DES and BMS cohorts using the Kaplan-Meier product limit estimate. Follow-up was censored at 24 months or on 30th June 2006 (if this date occurred first). Clinical outcome rates were derived from the Kaplan-Meier analyses. Probability statistics and hazard ratios comparing outcome for matched DES and BMS were derived from Cox-regression analyses stratified by matched pairs to account for the non-independence of groups, with type of stent

the sole predictor variable. The proportional hazards assumption was checked using the time varying coefficients method.[118] A p value of <0.05 was taken to indicate statistical significance. Propensity-score matching was carried out using the S-PLUS for Windows v7.0 software (Insightful Co. Seattle, WA, USA), while all other analyses were performed using SPSS for Windows v15.0 software (SPSS Inc, Chicago, Illinois, USA).

4.7. Results

Over the study period 11,317 patients had PCI with at least one stent inserted. Patients who received both a DES and BMS during the same procedure were excluded (639 or 5.6%) along with 332 (2.9%) patients who could not be linked to the outcome datasets. Of the remaining 10,346 patients, 7,499 (72.5%) fulfilled the "off-label" criteria and were thus included in the propensity score calculation. Of the patients defined as "off-label", 1,105 (14.7%) patients received a DES and 6,394 (85.3%) patients received a BMS. Marked differences in baseline clinical variables were noted between the BMS and DES groups. Table 11 summarises the differences in patient characteristics for those treated "off-label" prior to propensity-score matching. Figure 8 demonstrates the non-proportional event rates for MI following BMS and DES use prior to propensity score matching.

Table 11. All "off-label" patients: baseline characteristics prior to propensity matching

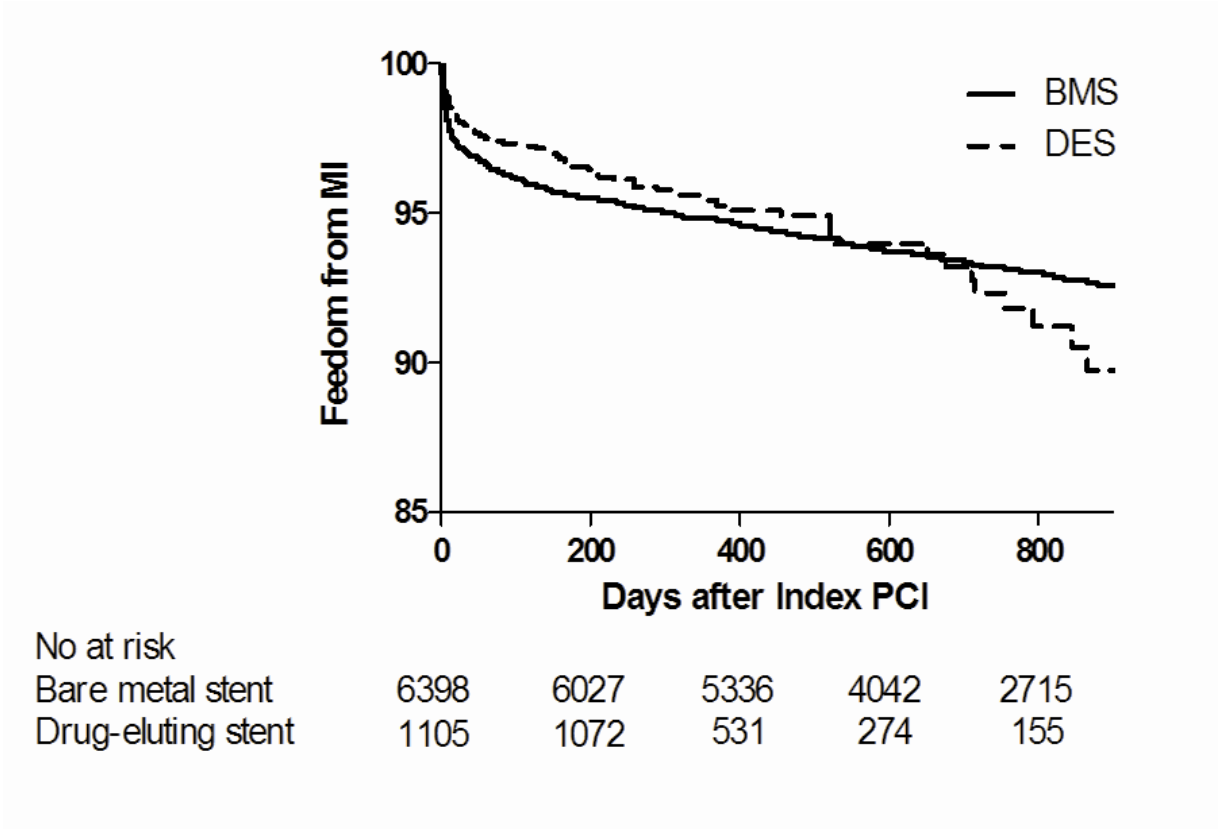
	Bare-metal stent n=6,394	Drug-eluting stent n=1,105	p value*
Age, years†	61.9 (10.8)	60.4 (10.8)	<0.001
Male, n (%)	4,671 (73.1)	760 (68.8)	0.003
Carstairs' deprivation quintile,n (%)			0.96
1	1,149 (18.5)	208 (19.4)	
2	1,275 (20.5)	209 (19.5)	
3	1,243 (20.0)	219 (20.4)	
4	1,210 (19.5)	211 (19.7)	
5	1,338 (21.5)	226 (21.1)	
Diabetes mellitus, n (%)	815 (13.3)	209 (19.6)	<0.001
Previous myocardial infarction, n (%)	2,098 (34.2)	357 (33.4)	0.8
Previous coronary artery bypass grafting, n (%)	663 (10.6)	118 (10.7)	0.87
Previous cerebro-vascular accident, n (%)	254 (4.2)	58 (5.5)	0.07
Peripheral vascular disease, n (%)	320 (5.4)	64 (6.1)	0.36
Chronic lung disease, n(%)	404 (6.9)	74 (7.1)	0.79
Renal dysfunction, n (%)	154 (2.6)	27 (2.6)	0.97
Left ventricular systolic dysfunction			<0.001
Mild-moderate	2,704 (44.8)	402 (39.1)	
Severe	128 (2.1)	17 (1.7)	
Indication for percutaneous coronary intervention			<0.001
Stable angina, n (%)	2,312 (37.1)	611 (56.9)	
Unstable angina, n (%)	1,215 (19.5)	180 (16.8)	
Non ST-elevation myocardial infarction, n (%)	1,832 (29.4)	217 (20.2)	
ST-elevation myocardial infarction, n (%)	873 (14.0)	66 (6.1)	
Procedure priority			<0.001
Elective, n (%)	2,399 (37.5)	643 (58.2)	
Urgent, n (%)	2,984 (46.7)	376 (34.0)	
Emergency, n (%)	1,011 (15.8)	86 (7.8)	
Number of lesions treated per procedure			<0.001
One lesion, n (%)	3,856 (60.3)	740 (67.0)	
Two lesions, n (%)	2,020 (31.6)	286 (25.9)	
Three or more lesions, n (%)	518 (8.1)	79 (7.1)	

Table 11 continued

Severity of coronary artery disease			0.02
Single vessel disease, n (%)	3,003 (49.6)	556 (52.8)	
Two vessel disease, n (%)	1,182 (19.5)	164 (15.6)	
Two vessel disease (with proximal LAD), n (%)	751 (12.5)	129 (12.2)	
Three vessel or left main coronary artery disease, n (%)	1,117 (18.5)	205 (19.4)	
Reference vessel diameter			<0.001
≤2.5 mm, n (%)	362 (6.0)	214 (20.2)	
2.6-3.0mm, n (%)	2,879 (47.8)	616 (58.2)	
3.1-3.5mm, n (%)	1,788 (29.7)	215 (20.3)	
>3.5mm, n (%)	999 (16.6)	13 (1.2)	
Stented length			<0.001
≤15mm, n (%)	1,845 (30.6)	107 (10.1)	
16-30mm, n (%)	3,169 (52.6)	543 (51.3)	
>30mm, n (%)	1,007 (16.7)	408 (38.6)	
Left main coronary artery, n (%)	121 (1.9)	70 (6.3)	<0.001
Bypass graft, n (%)	377 (5.9)	30 (2.7)	<0.001
Left anterior descending artery, n (%)	2,766 (43.3)	604 (54.7)	<0.001
Bifurcation lesion, n (%)	1,017 (15.9)	208 (18.8)	<0.001
Chronic total occlusion, n (%)	207 (3.2)	81 (7.3)	<0.001
Restenosis, n (%)	158 (2.5)	144 (13.0)	<0.001

*Chi squared test unless stated †Unpaired 2-sample t-test

Figure 8 Kaplan-Meier curves demonstrating freedom from myocardial infarction for "off-label" drug-eluting and bare-metal stent cohorts prior to propensity score matching



Propensity-score matching was successful in ensuring comparability of baseline clinical, demographic and angiographic co-variates (Table 12). No statistical differences were noted and calculated standardised differences were <3% between groups. The median propensity score was 0.35 (IQR 0.16-0.52) for the included DES population, and 0.35 (IQR 0.17-0.52) for the included BMS population. Thus the final study population contained 821 well matched pairs.

Of the final DES cohort, 513 received the paclitaxel-eluting Taxus stent (Boston Scientific Corp., Natlick, MA, USA), 275 received the sirolimus-eluting Cypher stent (Cordis Corp., Miami, FL, USA) and 33 patients received different DES for separate lesions within the same procedure. Of the BMS cohort, 78.6% received thin-strut or cobalt-chromium stents. We had follow-up data over a median of 16 months (range 9-24 months). During follow-up, there were 89 deaths, 99 MIs (54 non-fatal and 45 fatal) and 173 TVRs. No evidence of non-proportional hazards was found (mortality model, p=0.95; MI model, p=0.15).

Table 12. Propensity-score matched cohorts: baseline characteristics

	Bare-metal stent n=821	Drug-eluting stent n=821	p value*
Age, years†	60.6 (10.8)	60.8 (10.9)	0.63
Male, n (%)	557 (67.8)	569 (69.3)	0.56
Carstairs' deprivation quintile, n (%)			0.90
1	157 (19.6)	152 (19.0)	
2	165 (20.7)	167 (20.9)	
3	161 (20.2)	160 (20.0)	
4	153 (19.1)	151 (18.9)	
5	163 (20.4)	170 (21.3)	
Diabetes mellitus, n (%)	155 (18.9)	149 (18.1)	0.85
Previous myocardial infarction, n (%)	268 (32.6)	266 (32.4)	0.86
Previous coronary artery bypass grafting, n (%)	84 (10.2)	87 (10.6)	0.61
Previous cerebro-vascular accident, n (%)	39 (4.8)	39 (4.8)	0.68
Peripheral vascular disease, n (%)	53 (6.5)	45 (5.5)	0.66
Chronic lung disease, n(%)	47 (5.7)	53 (6.5)	0.45
Renal dysfunction, n (%)	27 (3.3)	22 (2.7)	0.88
Left ventricular systolic dysfunction			0.80
Mild-moderate	290 (35.3)	317 (38.6)	
Severe	12 (1.5)	12 (1.5)	
Indication for percutaneous coronary intervention			0.61
Stable angina, n (%)	401 (48.8)	406 (49.5)	
Unstable angina, n (%)	138 (16.8)	141 (17.2)	
Non ST-elevation myocardial infarction, n (%)	204 (24.8)	188 (22.9)	
ST-elevation myocardial infarction, n (%)	60 (7.3)	64 (7.8)	
Procedure priority			0.74
Elective, n (%)	420 (51.2)	429 (52.3)	
Urgent, n (%)	322 (39.2)	313 (38.1)	
Emergency, n (%)	79 (9.6)	79 (9.6)	
Number of lesions treated per procedure			0.79
One lesion, n (%)	525 (63.9)	517 (63.0)	
Two lesions, n (%)	226 (27.5)	235 (28.6)	
Three or more lesions, n (%)	70 (8.5)	69 (8.4)	

Table 12. continued

Severity of coronary artery disease			0.25
Single vessel disease, n (%)	375 (45.7)	410 (49.9)	
Two vessel disease, n (%)	144 (17.5)	125 (15.2)	
Two vessel disease (with proximal LAD), n (%)	109 (13.3)	101 (12.3)	
Three vessel or left main coronary artery disease, n (%)	193 (23.5)	185 (22.6)	
Reference vessel diameter			0.60
≤2.5 mm, n (%)	106 (13.7)	114 (14.7)	
2.6-3.0mm, n (%)	477 (61.9)	469 (60.4)	
3.1-3.5mm, n (%)	176 (22.8)	181 (23.3)	
>3.5mm, n (%)	12 (1.6)	13 (1.7)	
Stented length			0.40
≤15mm, n (%)	79 (10.2)	94 (12.1)	
16-30mm, n (%)	447 (58.0)	423 (54.4)	
>30mm, n (%)	245 (31.8)	260 (33.5)	
Left main coronary artery, n (%)	44 (5.4)	39 (4.8)	0.65
Bypass graft, n (%)	28 (3.4)	28 (3.4)	0.54
Left anterior descending artery, n (%)	429 (52.3)	434 (52.9)	0.84
Bifurcation lesion, n (%)	169 (20.6)	154 (19.4)	0.57
Chronic total occlusion, n (%)	40 (4.9)	49 (6.0)	0.39
Restenosis, n (%)	73 (8.9)	72 (8.8)	1.0

*****McNemar test unless stated †Paired 2-sample t-test

In the analysis of all-cause death, a higher overall fatality rate was observed among BMS treated patients (Figure 9, Table 13). Over the first 6 months, there was a higher rate of death among the BMS group but this was not statistically significant (4.1% vs. 2.9%, p=0.11). Beyond 6 months, case-fatality rates were similar (3.6% vs. 3.7%, p=0.21). Overall, the absolute difference between the groups was 1.1% (7.7% vs. 6.6%, Hazard ratio (HR) 0.63 95% confidence interval (CI) 0.40-0.99, p=0.04). No statistically significant difference in the rate of MI was noted during follow up (Figure 10, Table 3). MIs were numerically, though not statistically, more common following BMS during the first 6 months follow-up (4.8% vs. 3.7%, p=0.31). MIs were less common from six months to the end of follow up, but were non-significantly more common in the DES group (2.5% vs. 3.8%, p=0.17). At 24 months, the net effect was that rates of MI were similar (7.3% vs. 7.5%, HR 1.02 95% CI 0.69-1.54, p=0.92). The rate of TVR was lower among DES treated patients (Figure 11, Table 13). This was apparent at 6 months (7.1% vs. 4.8%, HR 0.66 95% CI 0.44-0.99, p=0.04) and sustained at two years follow-up (13.9% vs. 10.7, HR 0.67 95% CI 0.49-0.93, p=0.02). The absolute difference between BMS and DES arms was therefore 3.2% at two years, equating to a number needed to treat of 31 patients to prevent one TVR.

Table 13. Outcome at time intervals from index PCI for propensity-score matched drug-eluting and bare-metal stent cohorts

	Death		Myocardial Infarction		Target Vessel Revascularisation	
	BMS	**DES**	**BMS**	**DES**	**BMS**	**DES**
1 month (%)	2.4	1.8	2.8	2.4	1.3	1.1
6 months (%)	4.1	2.9	4.8	3.7	7.1	4.8
12 months (%)	5.3	3.5	5.7	5.0	11.4	7.7
24 months (%)	7.7	6.6	7.3	7.5	13.9	10.7

Figure 9

Kaplan-Meier curves demonstrating survival for "off-label" drug-eluting and bare-metal stent cohorts matched by propensity score

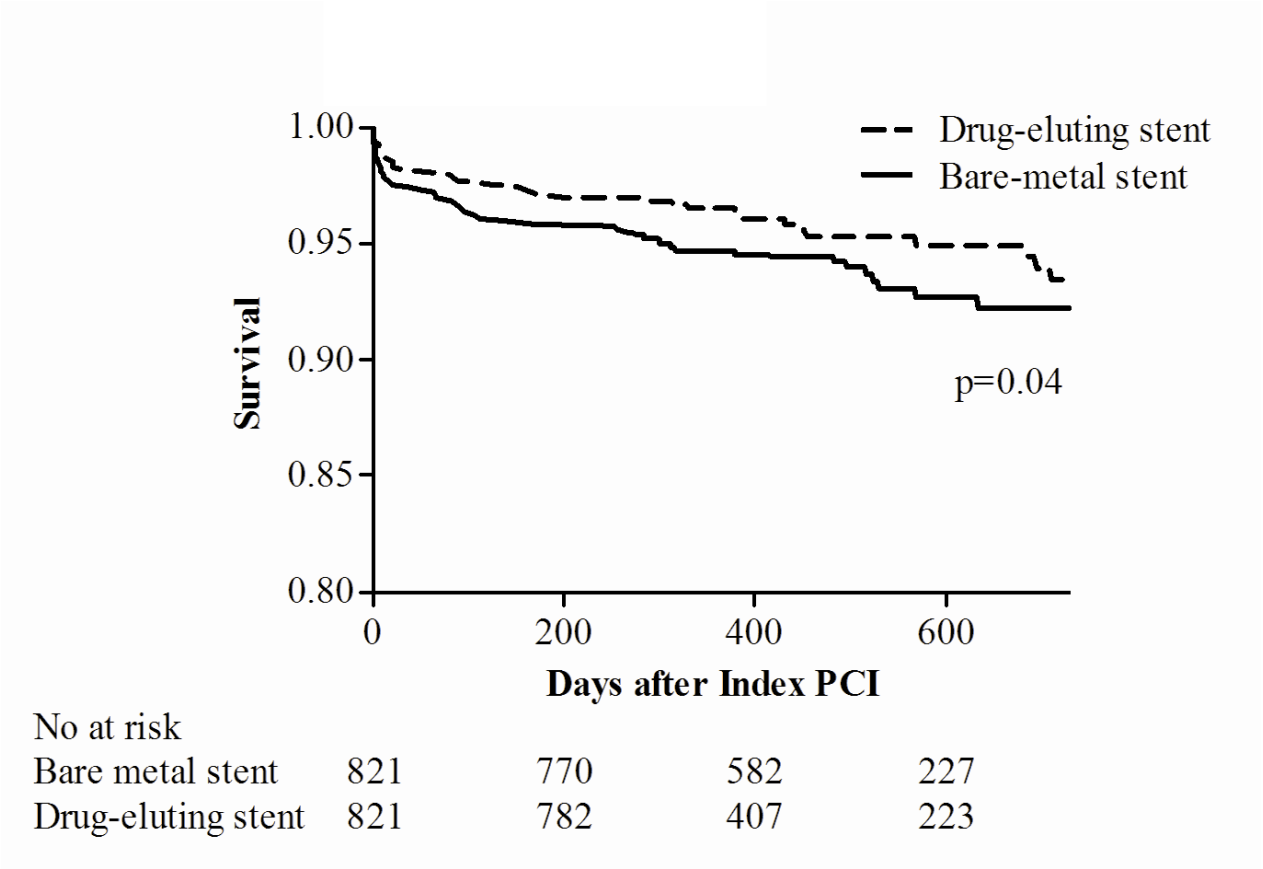
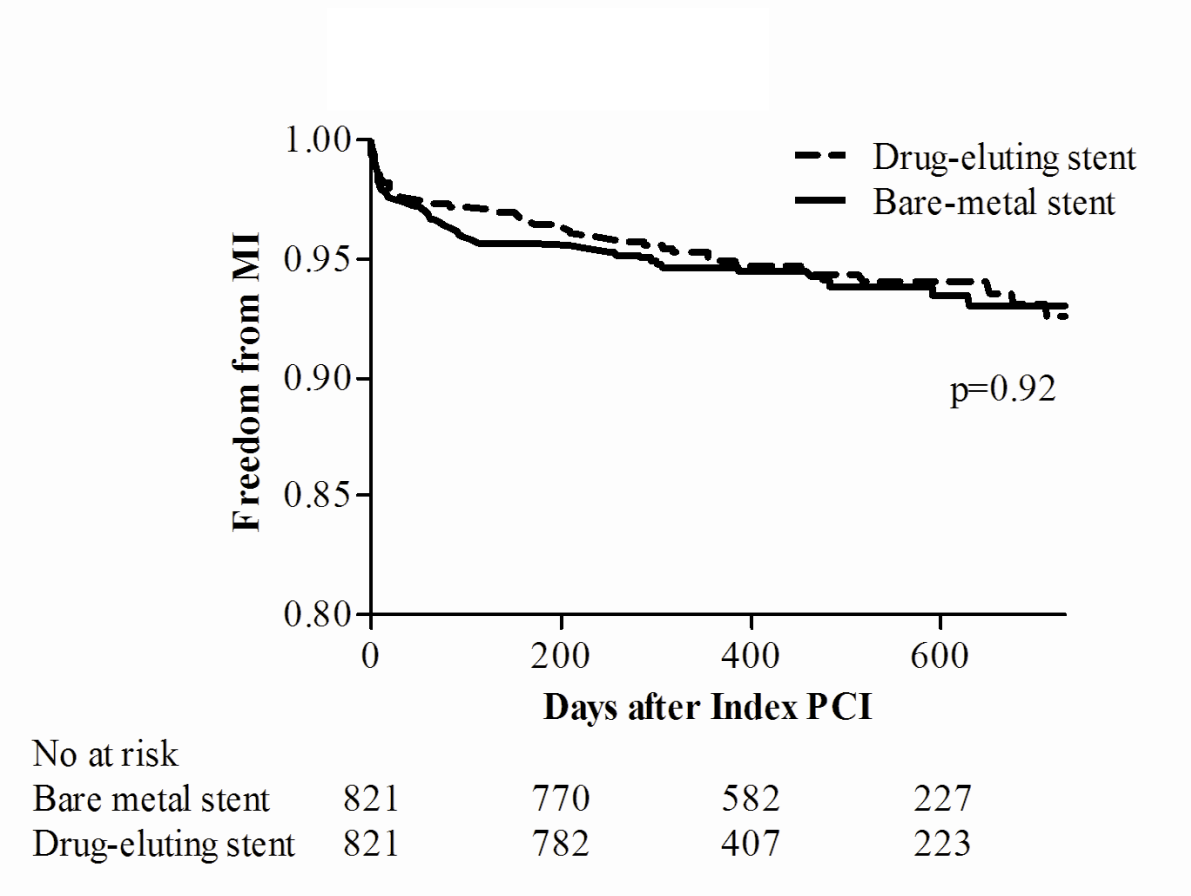


Figure 10

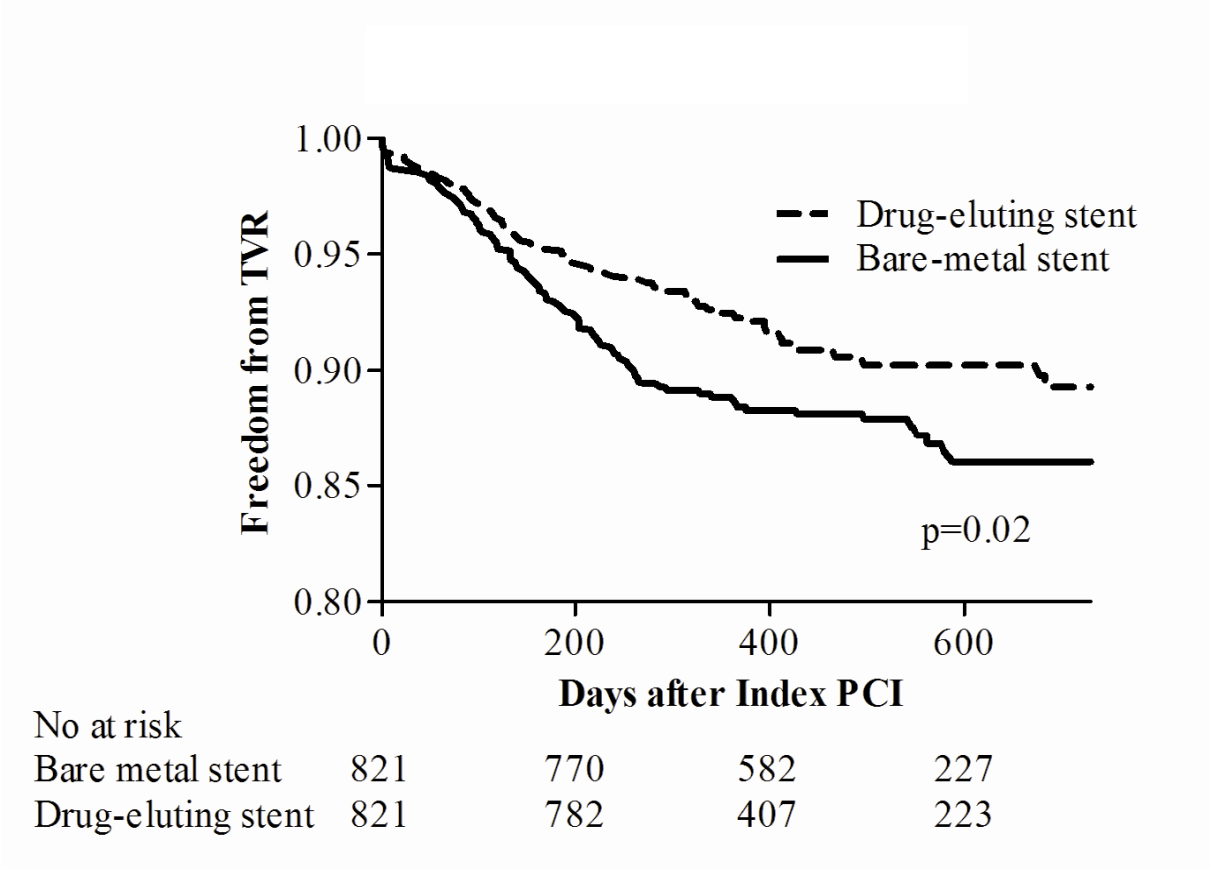
Kaplan-Meier curves demonstrating freedom from myocardial infarction for "off-label" drug-eluting and bare-metal stent cohorts matched by propensity score



No at risk				
Bare metal stent	821	770	582	227
Drug-eluting stent	821	782	407	223

Figure 11

Kaplan-Meier curves demonstrating freedom from target vessel revascularisation for "off-label" drug-eluting and bare-metal stent cohorts matched by propensity score



No at risk				
Bare metal stent	821	770	582	227
Drug-eluting stent	821	782	407	223

4.8. Discussion

In this study of "off-label" patients matched by propensity score, all-cause death was more common following BMS than DES and no difference was observed in the rates of MI. TVR was less frequent in patients treated with DES, with an absolute risk reduction of 3.2%.

Observational studies have compared unselected cohorts of BMS and DES[21,57,58,105] or outcomes in DES patients treated "off-label" and "on-label".[59,60] To date, three published studies have compared clinical outcomes between BMS and DES for "off-label" indications, although all were limited by the use of historical control groups (discussed in section 4.4).[107,108,129] This study is unique in comparing clinical outcomes over two years following DES with a contemporary BMS cohort in an "off-label" population.

"Off-label" use of DES is of great clinical importance. The FDA advisory panel meeting raised concerns about "off-label" use of DES as the RCT evidence in this area is sparse.[70] In the Scottish PCI population, "off-label" indications accounted for 72% of all PCIs. Worldwide this represents several hundred thousand interventions per year. This figure is higher than most other studies of "off-label" use[59,60,107] but was similar to Applegate et al.[108] who employed the same definition that included, for example, all patients with MI. The presence of thrombus may also be considered an off-label indication. This indication was not included as a separate entry criterion in this study, since all patients with thrombus also had other inclusion criteria (such as MI) and were thus already in the "off-label" group.

Given that DES use in "off-label" patients has become commonplace following the rapid adoption of these devices, the finding of no significant difference in MI at two

year follow up is therefore reassuring. Indeed, for the outcome of all-cause death there was a suggestion of reduced fatality following DES use. Tu et al. also observed such a difference in their study of unselected patients at three years follow up.[105] In this analysis, however, the observation was only of borderline statistical significance and it has not been evident in patient-level meta-analyses of predominantly "on-label" patients from randomized trials of relatively simple single de-novo lesions.[19,50-52,104]

An absolute reduction of 3.2% in TVR is considerably smaller than the difference demonstrated in RCTs.[4,5,17,18,22,24,25,31,32] Given the relative complexity and high baseline risk of restenosis in patients treated "off-label", this could be viewed as a surprisingly low benefit. However, most RCTs have used relatively thicker-strut stainless steel comparator stents and these have a high rate of restenosis when compared with thin-strut BMS.[130] In addition, the use of protocol-mandated angiography and the well described "oculo-stenotic reflex" within RCTs inflates the absolute difference between DES and BMS.[11]

In the UK, attempts to ration the use of DES and control overall costs are ongoing.[14] As a result of these financial considerations, use of thin-strut and cobalt-chromium BMS was commonplace during the study period, and provided control patients treated contemporaneously for a broad range of indications. The comparison of DES with modern BMS in a "real-world" setting is therefore a major strength of this current analysis. The finding of a 3.2% absolute risk reduction in TVR is comparable with the two year outcomes from the Ontario province.[105] Such findings may have implications in resource limited healthcare systems.

Although in this study there was insufficient power to undertake sub-group analysis of outcome by "off-label" characteristic, it is likely that the benefit of DES varies by subgroup. This aspect merits further study to assist ongoing efforts to target DES use in a cost-effective manner.

Follow-up information was ascertained via linkage to national administrative databases. Less than 3% of index cases could not be linked to the national dataset at baseline, and therefore follow-up information was not available. Missing linkage is unrelated to baseline patient characteristics and thus there is no reason to believe this introduces a systematic error to the analysis. Indeed, ascertainment of clinical end-points via this mechanism is well established and has been shown to be as complete as prospective follow-up.[127] The Scottish Morbidity Record does not record stent thrombosis, so this could not be reported as a separate outcome. It is also acknowledged that, in common with most registries, we lacked an independent clinical events committee, and angiographic core laboratory. The end-points of MI and death are, however, clinically pertinent, without reporting bias with respect to stent type and correspond with previous registry studies using data linkage.[57,58,105]

A previous observational study by Eisenstein et al. provided important insight into the potential role of clopidogrel in preventing adverse outcomes in DES but not BMS.[64] The clinical protocols active during the study recommended 6 months dual anti-platelet therapy following DES and between 1 and 3 months following BMS. However, duration of clopidogrel use was not recorded at patient level and therefore I cannot expand on this issue. Since the period of recruitment for this study recommended duration of dual anti-platelet therapy following DES has been empirically extended to one year.[70]

Observational studies comparing BMS and DES provide a challenge because of the pattern of events during follow up, i.e. higher early events with BMS, and higher late events with DES. Landmark analyses have been employed to elucidate late risks of DES and to allow the proportional risks assumption to be met.[21,57] Adjustment for baseline clinical risk is then possible. Such studies have highlighted the potential impact of late stent thrombosis in DES, though they may exaggerate the importance of late events and increase the sensitivity of such analyses to bias. Using propensity scores to match patients by clinical variables at baseline confers some of the inherent advantages of experimental study design; the actual pattern of clinical events is preserved and outcomes can be compared over the whole period of follow-up. Differences in observational design may partly explain the varying conclusions from DES outcome studies.

It was not possible to match 284 (25.7%) of "off-label" DES patients with an equivalent BMS control. The 284 excluded DES patients were inevitably at higher propensity scores, where the ratio of BMS to DES was lower. Of the excluded DES patients, 10% had left main coronary artery PCI, 52% had stented length greater the 30mm, 25% had restenosis and 11% had chronic total occlusions. Among the excluded DES patients, the median propensity score was 0.75 (IQR 0.68-0.84). This compares with 0.35 (IQR 0.16-0.52) for the included populations. Notably, where a DES to BMS match existed, both patients were included ensuring a wide range of propensity scores (0.002-0.946) within the study, representative of actual "off-label" practice. This wide range of propensity scores in the final study argues against a "trimming" procedure prior to matching and in favour of the "caliper width" method of matching that I employed.

As a consequence of the exclusions the statistical power of the study was reduced. For these patients, it is likely that the existence of DES technology influenced the decision to proceed with PCI, and for many a comparison with bypass surgery or

medical therapy would have been more appropriate. Thus, by excluding such DES treated patients the final subjects were a population for which selection bias was minimised and for whom a genuine choice between BMS and DES exists in current clinical practice.

As with all observational studies, it is accepted that there may be residual bias due to unknown or unmeasured factors, in particular co-variates relating to non-cardiac co-morbidity such as dementia and malignant disease which could potentially influence stent choice (e.g. if long durations of clopidogrel therapy are thought to be undesirable). Therefore, these results require corroboration by other studies and, in particular, RCTs.

4.9. Conclusion

In this analysis of "off-label" indications, death was lower among DES patients at 24 months, and no difference was seen in the rates of MI between matched BMS and DES cohorts. Propensity score matching was employed to provide the most accurate estimate of treatment effect and to minimise bias. A contemporary control group was drawn on to make the results relevant to current practice.

Given the importance of "off-label" indications and the wide acknowledgement of very late risks[55], longer term follow up is warranted. The benefits of DES were evident, though the absolute reduction in TVR was lower than previously demonstrated in RCTs.

5. Appropriate use of drug-eluting stents: a modified Delphi consensus study

In chapter 3, it was shown that usage of DES within the UK health care setting varies significantly by hospital and operator. As discussed in Chapter 3 where the best evidence based treatment is followed, logically variations should be minimal limited to legitimate sources of difference. However as one author, DM Eddy, writes

"The problem of course is that nothing is this simple. Uncertainty, biases, errors, and differences of opinions, motives, and values weaken every link in the chain that connects a patient's actual condition to the selection of a diagnostic test or treatment."[78]

In Chapter 2, the evidence for and against the routine use of DES in clinical practice was discussed and it was concluded that selecting the "correct" stent for the "correct" patient is not straightforward. Thus the observation that undesirable variation exists is likely to predominantly reflect a lack of consensus in the optimum application of DES within routine clinical practice.

Among many areas where uncertainty can encroach on clinical encounters, Eddy identifies the "*observation of outcomes"* as particularly important.[78] Natural variation among individuals to a treatment necessitates an "averaging" of outcome for groups considered similar when outcomes are assessed. Thus even when information is available, at best we can only talk in probabilities of risk and benefit.

In the case of DES, large amounts of data are available including RCTs and meta-analysis. However, as discussed in Chapters 2 and 4 even the results of these most robust studies may be justifiably questioned on a number of grounds. Providing further RCTs to conclusively address all issues would be costly, time consuming (5 or 10 year follow-up cannot be shortened) and involve a large number of patients. Furthermore, in the time taken to formulate, conduct, disseminate, and interpret the results of a RCT, standard practice may have moved on and its applicability may be limited. Added to this mix are nonrandomized trials, uncontrolled trials, clinical observations and

the multitude of variables that exist in any individual clinical scenario. Finally, for any treatment (including DES) the range of outcomes include positive (reduction in restenosis, the need for repeat procedures, reduction in angina and improvement in quality of life) and negative (a potentially catastrophic but poorly defined risk of late stent thrombosis, a perceived need to take longer durations of antiplatelet therapy with consequent increased bleeding tendency, and an overall greater cost) which need to be weighed despite imperfect, necessarily averaged outcome data.

It becomes clear that defining the best treatment for any patient is indeed fraught with uncertainty. As Eddy concludes

"*... the difficulty in measuring outcomes has three important implications: we are uncertain about the precise consequences of using a particular procedure for a particular patient; we cannot, over the short term at least, resolve this uncertainty; and whatever a physician chooses to do cannot be proved right or wrong*."[78]

5.1. Evidence based medicine and methods for reducing uncertainty

Uncertainty and the consequent variations in practice was a major driver in the paradigm shift towards evidence-based medicine over the past three decades. Evidence-based medicine as a concept is, of course, now widely accepted. One group of authors define the concept

"…evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.

...the practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research."[131]

Clinical guidelines have been developed to facilitate the integration of published research into clinical practice. Such guidelines use scientific evidence to generate

graded recommendations on the appropriate treatment of patients with a condition or group of conditions. In terms of defining best practice for DES, ESC and AHA guidelines have predominantly used inclusion criteria for RCTs as the basis for recommendations. As discussed at length in Chapter 4, much of clinical practice would be excluded with such narrow boundaries, and in any case DES have already been used more widely.

In the UK, NICE produced health technology assessments both of which concluded that DES should be used in patients with vessel diameter <3mm or lesion length >15mm.[13,14] The assessment process involved projecting the clinical effectiveness of DES from published research to those excluded from the studies, and cost effectiveness through assessment of audit data. By including cost as a variable, the emphasis of the process moved away from defining best practice into managing the potential extra cost of an expensive new technology. Many lesion subsets in whom DES were efficacious in the RCT setting were excluded from the guidance on the basis that the "real" benefit of DES in actual clinical practice was likely to be lower than in the RCTs. Furthermore, detailed guidance on clinically important lesion sub-types and clinical presentations was lacking.

Given the clinical complexity of this area, and the simplicity of the ultimate statement of recommendation, it is unsurprising that adherence to the NICE recommendations is so variable. Indeed as the issue of stent thrombosis risk is not addressed at all, the reading of such a document is unlikely to assist a practicing clinician in upholding the best principles of evidence-based medicine.

Given the fundamental uncertainties at work a different approach to applying the best evidence and reducing uncertainty and variation may be required. One potential solution that has received much interest, particularly in the field of coronary revascularization, is the Delphi Method.

5.2. The Delphi Method

The original Delphi method was established in the 1950s when the Rand Corporation, funded by the US Military, tried to find a way of establishing a reliable consensus forecast among a group of experts of future Soviet military planning. This was the original "Project Delphi" - named after the Oracle at Delphi in ancient Greece, known for its prophesising powers.[132] Since its original use, the method has been employed in many fields including industry, education, government and healthcare.

In the original Delphi method the key features of the process were[132]:

1. Anonymous collection of opinion from a group of experts
2. Controlled feedback
3. Output in the form of a group response

Despite its popularity, this form of the technique, and its variable application, had been heavily criticised for crude questionnaire design including ambiguous questions and answers, absence of validity testing, methods of reporting findings and the lack of a critical literature on the method itself.[133]

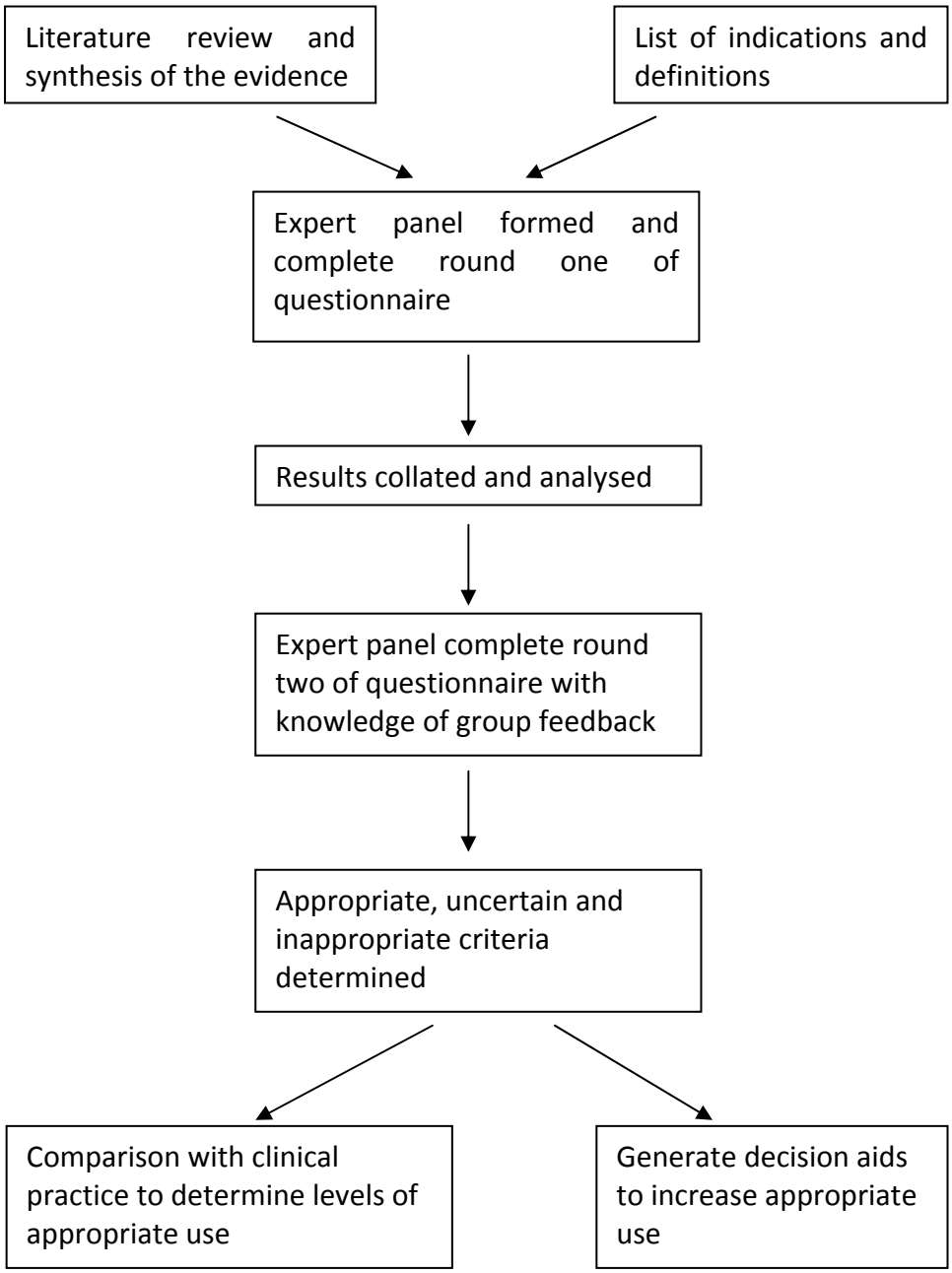
As discussed in section 5.0, modern clinical care is complex and the available evidence may not supply the necessary detail to guide daily practice. An awareness of this situation, and the criticisms of the original Delphi studies, led to the development of the RAND/UCLA appropriateness method.[134] This has been termed the modified Delphi method, and was specifically aimed at developing appropriateness criteria for medical procedures. The modified Delphi method is commonly used in areas of technical expertise where there is clinical controversy and evidence is contradictory or lacking. The development of this method was primarily to measure underuse and overuse of medical procedures, although clinical decision aids based on the method have also been developed.

Unlike the original studies, the modified Delphi method is a standardised process that has been extensively studied. A schematic overview of the modified Delphi methodology is shown in Figure 12.[134] There are many important differences in this modified process that address many of the criticisms directed towards original Delphi studies.

The first stage is to comprehensively review the published literature and synthesise the current evidence base. The expert panel are asked to base all judgements on the evidence provided. Where the modified Delphi method is applied to topics where a large scientific literature pertaining to outcome exists (from which the panel can extrapolate), it is more reliable. For example, it is thought to be particularly reliable in defining indications for coronary revascularisation but not hysterectomy.[135] The literature review is provided to the expert panel prior to the first round ratings.

Figure 12

Schematic diagram for the modified Delphi method



Following the literature review, a comprehensive list of clinical indications is developed. This list is based on the literature review and the establishment of clinical variables that physicians take into account when selecting treatment.[134] In this study, multivariate analyses of current PCI practice were available to aid this process (see Chapter 3). The list of indications should be comprehensive, mutually exclusive, and constitute a manageable number.[134] It is necessary to define each variable used in framing the clinical indications questionnaire to ensure each panel member is answering for the same homogenous indication.

The composition of the expert panel has also been examined. Multidisciplinary panels are favoured where a decision to perform a treatment is contributed to by a number of different specialties.[136] For example, a coronary revascularisation panel would include general non-invasive cardiologists, interventional cardiologists, cardiac surgeons and perhaps general physicians. In this study, however, only interventional cardiologists were selected for inclusion to reflect the realities of stent choice during a PCI procedure.

In the modified Delphi method panellists rate clinical indications on a 9-point Likert scale. The higher scores indicate a higher benefit-to-harm ratio for the treatment in question. The scores derived from this standardised questionnaire tool are used to feedback the group response, then later to define levels of agreement and overall appropriateness for each indication (see methods section below). A typical modified Delphi process occurs over 2 rounds, with interaction between panel members during the second round which typically (though not always) takes the form of a moderated face-to-face meeting.[134,137]

After the second round, final ratings are established. A clinical indication can be rated as appropriate, uncertain (which includes disagreement) or inappropriate. No attempt is made to force a consensus, other than to focus attention on uncertain indications or those with disagreement. In this area, the modified Delphi method

differs from other methods of developing consensus, such as the nominal group technique, which aim to establish a definitive answer.[137]

Ratings were designed to be used retrospectively to assess the level of over and underuse of medical procedures to aid healthcare planning. For this purpose the modified Delphi process has been used widely in the US in the field of coronary revascularisation.[138-140] One major criticism of original Delphi studies was the lack of measured validity of the panel findings.[133] The validity of panel judgements can be tested, however.

In a UK based study, Hemingway et al identified appropriate indications for angiography, PCI and CABG using a modified Delphi technique.[141] Subsequently, they prospectively collated data from patients newly diagnosed with stable coronary artery disease via rapid access chest pain clinics in London. Patients who underwent coronary angiography were then classified for analysis according to the panel recommendations (medical therapy, PCI or CABG), although clinical management proceeded without regard to the panel findings. Patients who were classified as "appropriate for CABG" but received medical therapy were four-times as likely (HR 4.08 (95% CI 2.82-5.93)) to suffer death or MI than those patients who received CABG. Similarly, patients classified as "appropriate for PCI" but received medical therapy were twice as likely (OR 1.97 (95% CI 1.29-3.00)) to have angina at follow up than those treated with PCI, though there was no difference in MI or death.[142] Interestingly, the latter finding is consistent with the subsequent COURAGE trial comparing medical therapy with PCI in stable angina.[143] Hemingway et al have also used panel ratings to develop decision aids for investigation and management of coronary artery disease as a method for reducing practice variations and improving evidence based care.[144]

5.3. Drug-eluting stents – the justification for consensus criteria

In RCTs, DES reduce restenosis following PCI when compared with BMS.[4,5,18,41] Arguments against universal DES use include a lower absolute benefit compared

with the patient populations in the RCTs,[11,13,14,105] concerns regarding late stent thrombosis,[21,55] and the need for a prolonged duration of dual antiplatelet therapy.[64]

Although the overall safety of DES among patients studied in RCTs was not compromised by late stent thrombosis,[70] it has been estimated that approximately two-thirds of patients treated in clinical practice would have been excluded from the original RCTs. Many patient and lesion criteria predictive of stent thrombosis were also exclusion criteria for RCTs, including treatment of bypass grafts[55], bifurcation lesions[21], and high-risk acute coronary syndromes.[20] Conversely, factors conferring a higher risk of restenosis following PCI (and therefore greater potential benefit with DES), such as very long coronary lesions, chronic total occlusions and restenotic lesions, were under represented.

Furthermore, many factors that influenced DES use in the real world fall outside of current guidance; these include diabetic status, treated vessel, clinical presentation and presence of restenosis. Thus, although significant practice variation exists, it is not clear whether, in any given setting, there has been underuse potentially forfeiting the benefits of DES or overuse where benefits may be outweighed by risks, resulting in an unjustified greater overall cost.

While the modified Delphi method has been employed in developing appropriate indications for different cardiovascular procedures[138-140,145] it has not before been used to establish appropriate stent choice during PCI. By employing the Delphi method, I have attempted to use a combination of the current evidence-base and pooled expert judgement to develop criteria for DES use. The appropriateness scores were used retrospectively to derive rates of expected DES use, analyse underuse and overuse of DES in actual practice, and prospectively to examine clinical outcomes and seek external validity for the panel findings.

5.4. Aims

The initial aim was to establish detailed clinical criteria for appropriate use of DES using the Delphi method.

Following the establishment of criteria for appropriate DES use, I aimed to derive rates of expected DES use in clinical practice and then compare the expected rates to actual clinical practice.

Finally, to externally validate the findings of our expert panel, I aimed to compare clinical outcomes in patients with appropriate lesions, treated with either a BMS or DES.

5.5. Methods

This study was performed in three parts. First, consensus criteria for the appropriate use of DES using the modified Delphi method were generated. Second, the consensus criteria were employed to estimate the rate of appropriate, uncertain and inappropriate lesions in clinical practice, and comparing these with actual DES use. For this analysis, a 12 month extract of data (July 2006-June 2007) from the Scottish Coronary Revascularisation Registry was employed. Finally, to externally validate the findings of the expert panel, earlier registry data (January 2003-June 2006) were used to analyse clinical outcomes for DES and BMS patients treated for appropriate indications.

5.5.1. Developing criteria for drug-eluting stents through the Delphi method

In the Delphi method an expert panel, usually of between 8 and 15 members, is employed to rate the appropriateness of an intervention for a comprehensive range of clinical indications. Unlike in the decision to proceed with angiography, PCI or CABG, the choice of DES or BMS during PCI is almost universally made by the interventional cardiologist at the time of procedure. Hence for this study of DES appropriateness, it was decided to assemble a panel of only interventional cardiologists.

Twenty-four interventional cardiologists from all regions of the UK were invited to participate with the aim of achieving a quorum for a Delphi expert panel (appendix II shows the invitation letter). Ten individuals agreed to participate and completed the process by July 2008. Expert opinion was gathered through a specially designed questionnaire tool. The questionnaire consisted of 568 mutually exclusive indications for PCI based on factors that affect stent choice derived from the published literature and previous analysis of DES use (fig 13). The questions were grouped into six chapters defined by clinical indication and diabetic status. The first round questionnaire can be viewed in appendix III.

5.5.1.1. Definitions for the Delphi questionnaire

For the purposes of the questionnaire, ST-elevation MI was defined as a primary or rescue PCI; non-ST elevation MI (or high risk acute coronary syndrome (ACS)) as PCI during or following a troponin-positive ACS; and stable angina or low risk ACS as PCI for symptomatic relief with no prognostic benefit expected. Diabetes mellitus comprised both type 1 and type 2 diabetes mellitus. Chronic total occlusions were defined as lesions present for more than 3 months presenting with stable symptoms. Restenosis was defined as a restenotic lesion within a BMS or following balloon angioplasty of a native vessel, presenting with stable symptoms.

5.5.1.2. Delphi panel process

In round 1, panellists were provided with a comprehensive literature review and asked to independently rate each indication for the appropriateness of DES use. In line with the modified Delphi method, experts were asked to use a combination of the best available scientific evidence and extrapolation from the evidence base to establish their ratings for each indication. Appropriate use was defined as the expected health benefit of using a DES rather than a BMS exceeding the expected negative consequences by a sufficient margin that the use of a DES was deemed worthwhile. An example of an indication from round 1 is shown with the rating scale (Figure 14).

Figure 13. Clinical categories forming the basis for the appropriateness questionnaire

- Clinical presentation
    - Stable angina or low risk acute coronary syndrome
    - Non-ST elevation of high risk acute coronary syndrome
    - ST-elevation MI
- Diabetic status
- Vessel/lesion type
    - Native vessel (excluding proximal LAD)
    - Proximal LAD
    - Bypass graft
    - Restenosis
    - Chronic total occlusion
    - Left main coronary artery
    - Bifurcation lesion
- Vessel diameter
    - <3mm
    - ≥3mm
- Lesion length
    - <30mm
    - ≥30mm
- Procedure

- Single lesion PCI
- Two lesions, single vessel PCI
- Two vessel PCI
- Three vessel PCI

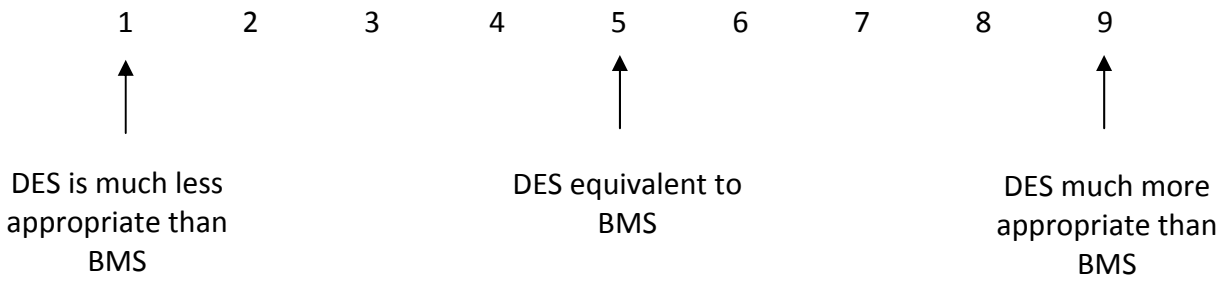
Figure 14

Example indication with nine-point (Likert) rating scale explained

Presentation: Stable angina

Non-diabetic

Native vessel, <3mm diameter, <30mm lesion, single lesion PCI



DES is much less appropriate than BMS

DES equivalent to BMS

DES much more appropriate than BMS

Panellists were asked to make a number of assumptions when rating each indication. The cost of stents and local and national rationing policies were to be disregarded. Ratings were to apply to an *average* patient, treated by an *average* physician, in an *average* hospital. For all indications, PCI with a stent was to be considered technically possible and alternative treatment strategies (i.e. CABG, isolated balloon angioplasty or medical therapy) were not to be considered. The type of DES and type of BMS to be used were assumed to be the most suitable for each indication. Finally, panellists were to assume no known contraindications to one-year dual anti-platelet therapy at baseline and average patient compliance.

Following the completion of round 1, for each of the 568 indications, all of the panellists' scores were pooled. The median score across all ten panellists was calculated and defined as inappropriate (median 1-3.5), uncertain (4-6) or appropriate (6.5-9) for the purposes of feedback. The level of agreement between panellists was also calculated using an empirically validated technique outlined by the RAND corporation/UCLA.[134] The formula employed mirrors the "classic" definition of disagreement based on a 9 member panel. The formula accounts for the spread of responses and adjusts for asymmetry. Figure 15 shows a worked example. This formula was applied to the set of 10 responses received for each indication to define "agreement" or "disagreement".

Panellists were then re-polled (round 2), this time having been provided with summary statistics derived from round 1. Each clinical indication had a reminder of the panellists' initial rating as well as the median score and level of appropriateness from round 1, and level of agreement between panellists (Figure 16). In round 2, the expert panel were encouraged to refine their judgement for each indication after considering the group response. Specific attention was drawn to uncertain indications or those with disagreement, although no attempt to force consensus was made. Appendix IV shows an extract from an individualised second round questionnaire.

Figure 15

Worked example to establish agreement/disagreement

IPR=Inter-percentile range (25-75%)

IPRr=Inter-percentile range required for disagreement when perfect symmetry exists

IPRAS=Inter-percentile range adjusted for asymmetry required for disagreement

AI=Asymmetry index

CFA=Correction factor for asymmetry

Indication 1

Rating Scale	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***
Panel frequencies		**2**	**1**	**1**	**2**	**3**		**1**	

Median Score 6.0 (Uncertain)

Step 1 Calculate IPR

Lower Limit (25%) 4.25

Upper Limit (75%) 7.0

IPR= 7.0-4.25= **2.75**

Step 2 Calculate central point of IPR

Central point of IPR=(7.0+4.25/2)=**5.625**

Step 3 Calculate AI

AI= Central point of IPR - Central point of scale

AI=5.625-5.0

AI=0.625

Step 4 Calculate IPRAS

IPRAS=IPRr+(AI*CFA)

Using the empirically derived values from RAND/UCLA, IPRr=2.35 and CFA=1.5.

IPRAS=2.35+(AI*1.5)

IPRAS=2.35+(0.625*1.5)

IPRAS=3.29

Step 5

If IPR<IPRAS then the indication is rated with agreement

If IPR>IPRAS then the indication is rated with disagreement

IPR=2.75

IPRAS=3.29

As IPR<IPRAS, the indication is rated as “with agreement”.

Figure 16

Example indication from round 2, with explanation of feedback

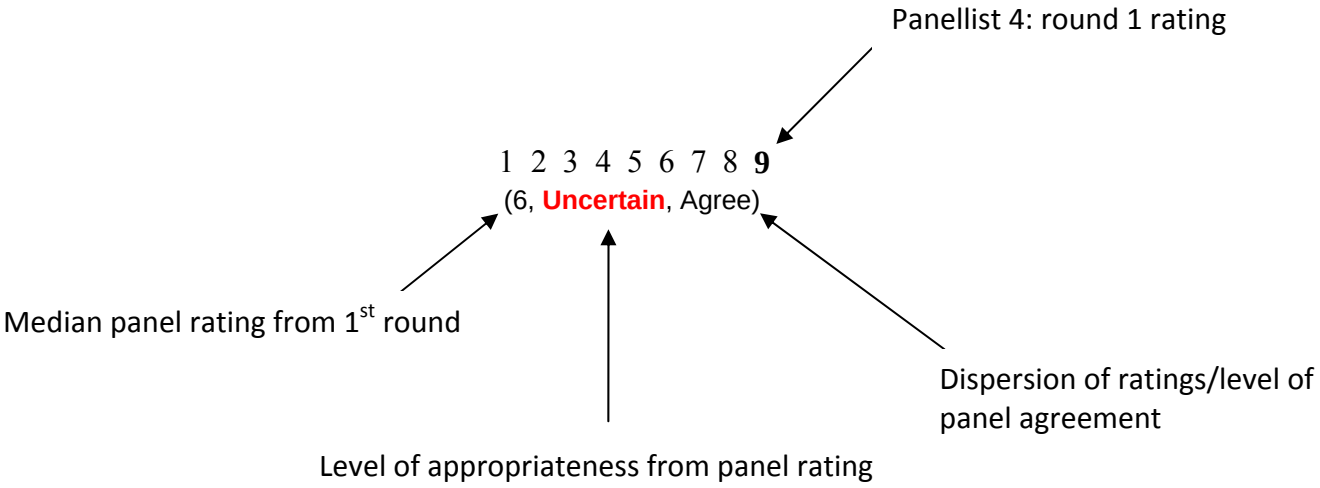
Panellist 3

Indication 1

Presentation: Stable angina

Non-diabetic

Native vessel, <3mm diameter, <30mm lesion, single lesion PCI



Following round 2, panellists' scores were again collated. Level of agreement between panellists was again established using the method described in figure 15. Final scores were determined and the final consensus view for use of a DES for each indication was defined as inappropriate (median 1-3.5), uncertain (4-6) or appropriate (6.5-9). If significant disagreement was present after round 2 the indication was rated as uncertain.

5.5.1.3. Statistical analysis

To assess the relative importance of individual clinical categories on determining panel rating the outcome was dichotomised to 'appropriate' (6.5-9) and 'not appropriate' (1-6). The dichotomised rating was entered as the dependent variable within a logistic regression model, with each clinical factor from the questionnaire (figure 13) a predictor co-variate. Adjusted odds ratios with 95% confidence intervals (CI) are reported.

5.5.2. **Comparison of Delphi consensus criteria to clinical practice**

5.5.2.1. Data sources

The Scottish Coronary Revascularization Register was used to provide detailed information for patients who underwent PCI. The register has been described in detail in section 3.3.2.1 and 3.4.3.1.

5.5.2.2. Study population and statistical analysis

Included in this analysis were consecutive patients treated with PCI over a 1 year period from 1st July 06- 30th June 07. To compare the established consensus criteria to clinical practice, Delphi clinical indications and their associated panel ratings were matched to lesions recorded in the Scottish Register. Expected rates of appropriate DES use were derived based on the Delphi questionnaire findings. The most frequently occurring appropriate, uncertain and inappropriate indications were determined.

Appropriateness criteria were then applied to the actual stent received. Overall DES use was derived for appropriate, uncertain and inappropriate indications. Within each appropriateness category, DES use by clinical subgroup was examined. Proportions treated with DES by clinical subgroup were compared with the proportion treated within the whole category.

Finally, the independent predictors of DES use in clinical practice within the lesions defined as appropriate and inappropriate were determined. For these analyses, logistic regression was employed with DES use the binary dependent variable. Covariates in the analysis were the clinical categories defined in the questionnaire (figure 13) and entered *a priori* into the equation. Model fit, tested using the Hosmer-Lemeshow statistic, and was found to be acceptable in both models. Predictive ability was 0.71 (appropriate model) and 0.66 (inappropriate model) when measured by the c-statistic. Proportions and odds ratios are presented with 95% confidence intervals.

5.5.3. Analysis of clinical outcomes

5.5.3.1. Outcome data and definitions

The final part of the analysis examined clinical outcomes following PCI with a BMS or DES in those patients defined as appropriate for DES. Clinical outcomes for the Scottish Coronary Revascularisation Registry are derived by linking to external datasets for hospital discharge information and death certifications, and within-registry internal linkage to determine repeat PCI on a target vessel. This process has been described in detail in section 4.6.1. Clinical outcome data were available up to 30th June, 2007.

5.5.3.2. Study Population

The analysis of clinical outcomes included patients if they underwent an index PCI between January 2003 and June 2006 inclusive, during which they had ≥1 stent inserted for an indication considered appropriate, according to the modified Delphi

panel, for a DES. Patients were excluded from this analysis if they could not be attributed to a specific indication in the Delphi questionnaire, could not be linked to the follow-up datasets, had received both DES and BMS within the same procedure, or had either an uncertain or inappropriate lesion treated within the same procedure.

5.5.3.3. Statistical Analysis

Among the patients who were treated for an appropriate indication, the baseline clinical and demographic characteristics varied significantly between those treated with DES and BMS. To allow meaningful analysis of clinical outcomes, a propensity score matching approach was adopted for those receiving a DES rather than a BMS.[119] For each patient a propensity score was calculated using baseline covariates within a logistic regression model. This baseline model included demographic and clinical covariates selected *a priori* for entry based on the potential influence on outcome (death, MI or TVR) if not uniformly distributed between groups. Table 23 lists the factors that were included in the baseline propensity score model and includes all factors that were present in the Delphi questionnaire.

Patients were matched according to their individual propensity scores on a 1:1 "nearest neighbour" basis using a calliper width of 0.2 times the standard deviation of the propensity score. A sensitivity analysis of hidden bias was conducted using Rosenbaum bounds.[119] This analysis essentially tests the influence of unobservable characteristics that could affect the assignment into treatment and outcome simultaneously.

During the study period, January 2003-June 2006, DES were being increasingly adopted into clinical practice. Following preliminary analysis, it was clear that a longer duration of follow-up for clinical events was available in the BMS group. Therefore the potential for follow-up bias existed due to the variation in the selection of patients over time for DES and BMS. To assess for the potential of

follow-up bias the event rates at 18 months – a point where follow-up was equal between groups - were calculated. Event rates up to 24 months were also calculated to provide information on an extended period (with the caveat of slightly uneven follow up between groups).

Categorical data were compared using the X^2 test (unmatched) or McNemar test (matched). Continuous data were compared using the 2-sample *t* test (unmatched) or paired 2-sample *t* test (matched) and expressed as mean (SD). The cumulative probability of outcome-free survival was determined separately for death, MI, and TVR for matched DES and BMS cohorts using the Kaplan-Meier product-limit estimate. Follow-up was censored at 30th June 2007. Clinical outcome rates were derived from the Kaplan-Meier analyses. Probability statistics and hazard ratios comparing outcome for matched DES and BMS were derived from Cox-regression analyses stratified by matched pairs to account for the non-independence of groups, with type of stent as the sole predictor variable. The proportional hazards assumption was checked by using the time varying coefficients method. A probability value of <0.05 was taken to indicate statistical significance. Propensity score matching and Rosenbaum sensitivity was conducted using Stata, v9.2 (Stata Corp., College Station, TX, USA). All other analyses were performed with SPSS for Windows v15.0 software (SPSS Inc, Chicago, Ill).

5.6. Results

5.6.1. Delphi Panel and Questionnaire

Twenty-four interventional cardiologists representing all regions of the UK (Scotland (4), Wales (2), England - North-East (2), North-West (2), Yorkshire (1), Midlands (4), London and the South (9)) were invited to participate in the process. Twelve (50%) initially agreed to participate, however two failed to complete the first round questionnaire and the process continued with ten experts (42%) who completed both rounds. This exceeded the minimum requirement for a Delphi panel. Panellists

who completed the final questionnaire were based in Scotland (4), Wales (1), North West England (2), The Midlands (1) London and South England (2). All ten panel members participated in both rounds and provided ratings to all 568 clinical indications. All second round questionnaires were completed by July 2008.

After the completion of round 2, of the 568 clinical indications, 364 (64.1%) were appropriate for DES, 155 (27.3%) uncertain and 49 (8.6%) inappropriate for DES. The overall median score was 7.0 (inter-quartile range (IQR) 5.5-8.0). Among indications considered appropriate for DES the median score was 8.0 (IQR 7.0-9.0). For indications within the uncertain category, the median was 5.5 (IQR 4.5-6.0) and for inappropriate indications 3.0 (2.5-3.0).

There was a high level of consistency between the panellists. At the end of round 1, panellists disagreed on 47/568 indications (8.3%). The level of disagreement reduced to 11/568 indications (1.9%) following the completion of round 2.

Table 14 outlines the relative importance of individual clinical categories on the panel ratings. For the multivariate analysis, restenosis and CTO were excluded, because all 64 clinical indications that featured these variables were rated as appropriate.

All clinical factors were statistically significant multivariate predictors of binary appropriateness with the exception of two lesion, single vessel and two vessel PCI (Table 14). There was however a trend whereby the probability of an indication being rated as appropriate for DES increased with increasing numbers of lesions/vessels treated per procedure (linear-by-linear association, p=0.036). The

strongest predictors of panel rating (based on Wald statistic) were STEMI, large vessel diameter and bypass graft lesion, all of which increased the likelihood of an indication receiving a “not appropriate” rating. Lesion length and diabetes were the strongest predictors of an appropriate rating.

Table 14. Effect of clinical, lesion and procedural factors on questionnaire appropriateness rating

CLINCAL SUBGROUP*	Univariate		Multivariate	
	Odds ratio (±95%CI)	p value	Odds ratio (±95%CI)	p value
CLINICAL INDICATION FOR PCI				
NON-STEMI/HIGH RISK ACS	0.70 (0.43-1.13)	0.001	0.42 (0.20-0.90)	0.026
STEMI	0.16 (0.09-0.25)	<0.001	0.01 (0.004-0.03)	<0.001
DIABETIC STATUS			9.77 (4.94-19.33)	<0.001
DIABETIC	2.39 (1.66-3.44)	<0.001		
LESION TYPE‡				
PROXIMAL LAD	2.33 (1.26-4.31)	0.007	7.12 (2.68-18.88)	<0.001
BYPASS GRAFT	0.18 (0.094-0.35)	<0.001	0.21 (0.007-0.64)	<0.001
LMCA	1.30 (0.52-3.25)	0.58	9.32 (2.00-43.05)	0.005
BIFURCATION	2.15 (1.29-3.60)	0.004	5.91 (2.58-13.54)	<0.001
VESSEL DIAMETER				
≥3mm	0.23 (0.15-0.33)	<0.001	0.02 (0.01-0.06)	<0.001
LESION LENGTH				
≥30mm	2.33 (1.62-3.37)	<0.001	10.80 (5.31-21.97)	<0.001
PROCEDURE				
TWO LESIONS, SINGLE VESSEL	1.02 (0.62-1.66)	0.946	1.21 (0.52-2.81)	0.666
TWO VESSEL PCI	1.17 (0.71-1.66)	0.539	1.76 (0.75-4.14)	0.196
THREE VESSEL PCI	1.50 (0.91-2.47)	0.113	3.51 (1.45-8.51)	0.006

*Odds ratios are referent to stable angina (clinical indication), non-diabetic, native vessel PCI (lesion type), vessel diameter <3mm, lesion length <30mm, and single lesion procedure
‡CTO and restenosis are not included in the multivariate model as all indications are rated appropriate

5.6.2. Comparison of Delphi consensus criteria to clinical practice

The Scottish Coronary Revascularisation Registry recorded 7,788 lesions treated with PCI with a stent from July 2006 to June 2007. There were 1,339 lesions (17.2%) with one or more missing variables that prevented the mapping of a Delphi clinical indication. After excluding patients with missing data 6,395 lesions (99.1%) were successfully matched to a clinical indication from within the questionnaire. Of these lesions, 2,673 (41.8%) were appropriate, 1,384 (21.6%) were uncertain, 2,338 (36.6%) were inappropriate indications for DES. Table 15 cross-tabulates the clinical categories included in the questionnaire with the expected level of DES use, as defined by the Delphi appropriateness scores. These results reflect the overall findings of the Delphi questionnaire; though add the weighting of the varying frequency with which indications occur in actual PCI practice.

Individual Delphi clinical indications occurred with varying frequency within actual clinical practice. 324 (57.0%) of the Delphi indications were treated in clinical practice during the 12 month period surveyed. By examining the ten most common indications within each appropriateness category an insight can be gained into the detail contained within the Delphi indications. Table 16 outlines the 10 most commonly occurring appropriate indications for DES use in the 12 month period. As treatment of CTO and restenotic lesions were considered appropriate under all clinical circumstances, these were listed as single variables. Table 17 and Table 18 outline the ten most common uncertain and inappropriate indications for DES. The most common individual indication represented 559 (8.7%) of the total lesions treated (Table 18). The second most common indication represented 250 (3.9%) of the total lesions treated (Table 17).

The indications listed in tables 16-18 account for 4,087 lesions (63.9%) of all treated lesions in the 12 month period, and 1,310 (49.0%), 794 (57.4%), and 1,983 (83.0%) of appropriate, uncertain and inappropriate indications respectively.

Table 15 Expected DES use based on DES appropriateness rating

CLINCAL SUBGROUP	n	APPROPRIATE n (%)	UNCERTAIN n (%)	INAPPROPRIATE n (%)
OVERALL	6395	2673 (41.8±1.2)	1384 (21.6±1.0)	2338 (36.6±1.1)
CLINICAL INDICATION FOR PCI				
STABLE ANGINA/LOW-RISK ACS	3989	2029 (50.9±6.0)	782 (19.6)	1178 (29.5)
NON-STEMI/HIGH RISK ACS	1509	629 (41.7±2.5)	378 (25.0)	502 (33.3)
STEMI	897	15 (1.7±2.4)	224 (25.0±2.8)	658 (75.9±2.9)
DIABETIC STATUS				
DIABETIC	964	803 (83.3±2.4)	112 (11.6±2.0)	49 (5.1±1.4)
NON-DIABETIC	5431	1870 (34.3±1.3)	1272 (23.4±1.1)	2289 (42.1±1.3)
LESION TYPE				
NATIVE VESSEL	3135	643 (39.7±1.4)	480 (11.6±1.3)	2012 (48.7±1.7)
PROXIMAL LAD	1028	419 (40.8±3.0)	504 (49.0±3.1)	105 (10.2±1.8)
BYPASS GRAFT	173	13 (7.5±3.9)	144 (83.2±5.6)	16 (9.2±4.3)
RESTENOSIS	152	152 (100)	-	-
CTO	247	247 (100)	-	-
LMCA	101	24 (23.5±8.3)	75 (73.5±8.5)	2 (2±2.7)
BIFURCATION	558	175 (31.4±3.9)	181 (32.4±3.9)	202 (36.9±4.0)
VESSEL DIAMETER				
<3mm	2046	1750 (85.5±1.5)	274 (13.4±1.5)	22 (1.1±0.5)
≥3mm	4371	923 (21.2±1.2)	1110 (25.5±1.3)	2316 (53.3±1.5)
LESION LENGTH				
<30mm	4938	1814 (36.7±1.3)	906 (18.3±1.1)	2218 (44.9±1.4)
≥30mm	1457	859 (59.0±1.1)	478 (32.8±0.8)	120 (8.2±0.4)
PROCEDURE				
SINGLE LESION	3488	1212 (34.7±1.6)	898 (25.7±1.5)	1378 (39.5±1.6)
TWO LESIONS, SINGLE VESSEL	1385	623 (45±2.6)	212 (15.3±1.9)	550 (39.7±2.6)
TWO VESSEL PCI	1344	733 (54.5±2.6)	208 (15.5±1.9)	403 (30.0±2.4)
THREE VESSEL PCI	178	105 (59.0±7.2)	66 (37.1±7.1)	7 (3.9±2.9)

Table 16. Most frequent appropriate indications for DES in clinical practice

Indication		Appropriateness score	Lesions, n (%) n=2673
Stable angina, non-diabetic, native vessel (not prox. LAD), <3mm vessel, <30mm lesion	Single lesion PCI	6.5	220 (8.2)
	Two lesion, single vessel	6.5	137 (5.1)
	Two vessel PCI	7	174 (6.5)
Non-STEMI, non diabetic, native vessel (not prox. LAD), <3mm vessel, <30mm lesion	Single lesion PCI	7	107 (4.0)
	Two lesion, single vessel	7	75 (2.8)
	Two vessel PCI	7	58 (2.2)
Stable angina, non-diabetic, native vessel (not prox. LAD), >3mm vessel, ≥30mm lesion	Two lesion, single vessel	6.5	64 (2.4)
Stable angina, non-diabetic, prox LAD , <3mm vessel, <30mm lesion	Single lesion PCI	7	64 (2.7)
Stable angina, diabetic, native vessel (not prox. LAD), <3mm vessel, <30mm lesion	Single lesion PCI	6.5	70 (2.6)
Restenosis		9	152 (5.7)
Chronic total occlusion		9	247 (9.2)
Total			1310 (49.0%)

Table 17. Most frequent uncertain indications for DES in clinical practice

Indication		Appropriateness score	Lesions, n (%) N=1384
Stable angina, non-diabetic, prox. LAD, ≥3mm vessel, <30mm lesion	Single lesion PCI	4.5	202 (14.6)
	Two lesion, single vessel	5	46 (3.3)
	Two vessel PCI	5	64 (4.6)
Stable angina, non-diabetic, native vessel (not prox LAD), ≥3mm vessel, ≥30mm lesion	Single lesion PCI	5.5	143 (10.3)
NSTEMI, non-diabetic, prox. LAD, ≥3mm vessel, <30mm lesion	Single lesion PCI	4.5	88 (6.4)
NSTEMI, non-diabetic, native vessel (not prox LAD), ≥3mm vessel, ≥30mm lesion	Single lesion PCI	5.5	87 (6.3)
	Two lesion, single vessel	5.5	41 (3.0)
STEMI, non-diabetic, native vessel (not prox LAD), <3mm vessel, <30mm lesion	Single lesion PCI	4	53 (3.8)
Stable angina, non-diabetic, bifurcation lesion, main branch <3mm, >30mm lesion	Single lesion PCI	6	37 (2.7)
Stable angina, non-diabetic, ostial/shaft LMCA, <4mm artery	Single lesion PCI	6	(2.4)
Total			794 (57.4)

Table 18. Most frequent inappropriate indications for DES in clinical practice

Indication		Appropriateness score	Lesions, n (%) N=2388
Stable angina, non-diabetic, native vessel (not prox LAD), ≥3mm vessel, <30mm lesion	Single lesion PCI	3	559 (23.9)
	Two lesion, single vessel	3	249 (10.7)
	Two vessel PCI	3.5	250 (10.7)
NSTEMI, non-diabetic, native vessel (not prox LAD), ≥3mm vessel, <30mm lesion	Single lesion PCI	2.5	221 (9.5)
	Two lesion, single vessel	3	113 (4.8)
	Two vessel PCI	3.5	113 (4.8)
STEMI, non-diabetic, native vessel (not prox LAD), ≥3mm vessel, <30mm lesion	Single lesion PCI	2	216 (9.2)
STEMI, non-diabetic, native vessel (not prox LAD), ≥3mm vessel, ≥30mm lesion	Single lesion PCI	3	92 (3.9)
Stable angina, non-diabetic, bifurcation lesion, main branch ≥3mm vessel, <30mm lesion	Single lesion PCI	3	88 (3.8)
STEMI, non-diabetic, prox. LAD, ≥3mm vessel, <30mm lesion	Single lesion PCI	3	82 (3.5)
Total			1983 (83.0)

5.6.3. Actual DES use in clinical practice compared with appropriateness criteria

During the 12 month period, DES were used in 3,203 (50.1%) lesions. There was a linear relationship between panel appropriateness rating and rates of actual DES use (linear-by-linear association $p<0.001$). Figure 17 shows the comparison of actual rate of DES use in lesions classified by appropriateness. When compared with the appropriateness criteria, 1,968 (73.6%) of appropriate lesions were treated with DES. Figure 18 and Table 19 outline the crude rate of DES use for lesions graded as appropriate. Following adjustment for all the clinical variables included in the questionnaire, use of DES for an appropriate lesion in clinical practice was statistically more likely for diabetic patients, restenosis, CTO, proximal LAD, LMCA and bifurcation lesions (versus native vessel PCI), small vessels, long lesions and increasing procedure complexity (Table 20). Use of a DES was relatively less likely in bypass graft lesions considered appropriate.

545 (23.3%) of lesions that were graded as inappropriate received a DES. Figure 19 and Table 19 show the rate of DES use in clinical practice among patients considered inappropriate for a DES (indicating potential "overuse" of DES). This figure also demonstrates the breakdown by clinical subgroup that can be compared to the overall rate among inappropriate lesions. Following adjustment for all the clinical variables included in the questionnaire using logistic regression, use of DES for inappropriate lesions was statistically more likely for diabetic patients, proximal LAD, bypass graft, bifurcation, long lesions and for multi-lesion procedures (Table 20). STEMI patients and larger vessel PCI were observed to be less likely to receive a DES inappropriately (Table 20).

Figure 17 Use of drug-eluting stents, by appropriateness ratings (% lesions +/- 95% CI)

Indication	DES/Lesions	Lesions (+/-95% CI)
Inappropriate	545/2388	23.3 (21.6-25.0)
Uncertain	691/1389	49.8 (47.1-52.4)
Appropriate	1968/2673	73.6 (72.0-75.3)

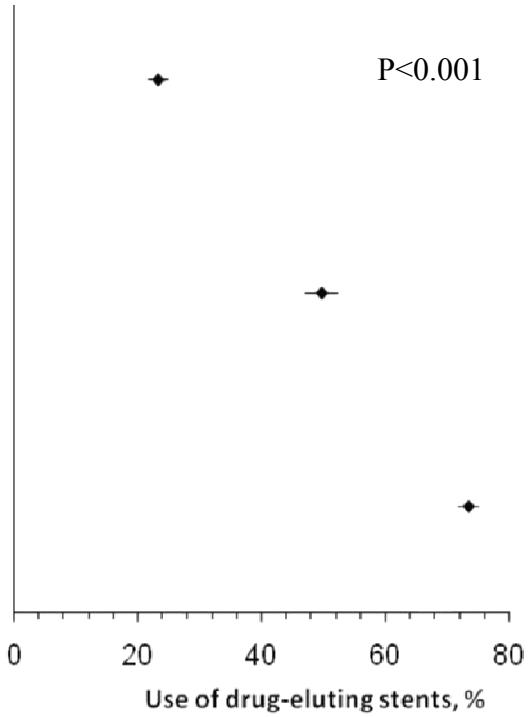


Figure 18 Rate of DES use for appropriate indications by clinical subgroup (%±95% CI)

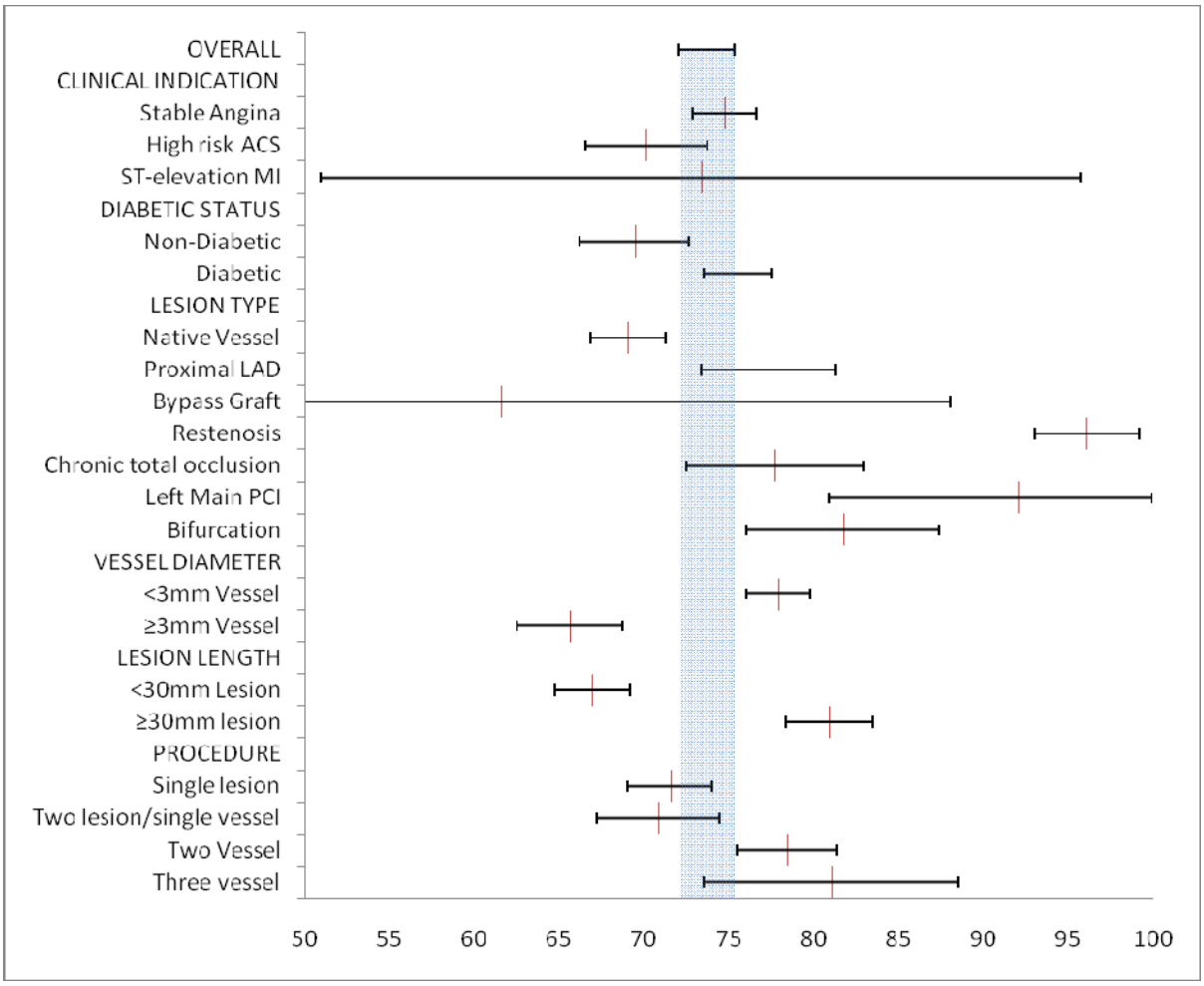


Table 19. Lesions treated with DES by appropriateness and clinical categories

CLINCAL SUBGROUP	APPROPRIATE DES/LESIONS (%±95% CI)	UNCERTAIN DES/LESIONS (% ±95% CI)	INAPPROPRIATE DES/LESIONS (% ±95% CI)
OVERALL	1968/2673 (73.6±1.6)	691/1389 (49.8±2.6)	545/2388 (23.3±1.7)
CLINICAL INDICATION FOR PCI			
STABLE ANGINA/LOW-RISK ACS	1516/2029 (74.7±1.9)	393/782 (50.3±3.5)	309/1178 (26.2±2.5)
NON-STEMI/HIGH RISK ACS	441/629 (70.1±3.6)	174/375 (46.4±5.1)	116/502 (23.1±3.7)
STEMI	11/15 (73.3±22.4)	124/224 (55.4±6.5)	120/658 (18.2±5.0)
DIABETIC STATUS			
DIABETIC	557/803 (69.4±3.2)	54/112 (48.2±9.3)	13/49 (26.5±12.4)
NON-DIABETIC	1411/1870 (75.5±2.0)	637/1272 (50.1±2.8)	532/2289 (23.3±1.8)
LESION TYPE			
NATIVE VESSEL	1133/1645 (69.0±2.2)	272/480 (57±4.4)	433/2012 (21.5±1.8)
PROXIMAL LAD	324/419 (77.3±4.0)	184/504 (36.5±4.2)	23/105 (21.9±7.9)
BYPASS GRAFT	8/13 (61.5±26.5)	62/144 (43.1±8.1)	7/16 (43.8±24.3)
RESTENOSIS	146/152 (96.1±3.1)	-	-
CTO	192/247 (77.7±5.2)	-	-
LMCA	22/24 (92±11.1)	55/75 (73.3±10.0)	1/3 (33.3±55.3)
BIFURCATION	143/175 (81.7±5.7)	118/181 (65.2±6.9)	81/202 (40.1±6.8)
VESSEL DIAMETER			
<3mm	1363/1750 (77.9±1.9)	186/274 (67.9±5.5)	12/22 (54.5±20.8)
≥3mm	605/923 (65.6±3.1)	505/1110 (45.5±2.9)	533/2316 (23.0±1.7)
LESION LENGTH			
<30mm	1273/1814 (66.9±2.2)	420/906 (46.4±3.3)	1273/1814 (22.8±1.8)
≥30mm	695/859 (80.9±2.6)	271/478 (56.7±4.4)	40/120 (33.3±8.4)
PROCEDURE			
SINGLE LESION	867/1212 (71.5±2.5)	419/898 (46.7±3.3)	258/1378 (18.7±2.1)
TWO LESIONS, SINGLE VESSEL	441/623 (70.8±3.6)	129/212 (60.8±6.6)	175/550 (31.8±3.9)
TWO VESSEL PCI	575/733 (78.4±3.0)	117/208 (56.3±6.7)	112/403 (27.8±4.4)
THREE VESSEL PCI	85/105 (81.0±7.5)	26/46 (39.4±11.8)	0/7 (0%)

Table 20. Adjusted use of DES for appropriate and inappropriate indications

CLINCAL SUBGROUP*	APPROPRIATE		INAPPROPRIATE	
	Odds ratio (±95%CI)	p value	Odds ratio (±95%CI)	p value
CLINICAL INDICATION FOR PCI				
NON-STEMI/HIGH RISK ACS	1.13 (0.92-1.38)	0.24	0.83 (0.64-1.07)	0.14
STEMI	0.30 (0.09-1.03)	0.06	0.34 (0.24-0.47)	<0.001
DIABETIC STATUS				
DIABETIC	2.20 (1.74-2.79)	<0.001	3.16 (1.55-6.46)	<0.001
LESION TYPE				
PROXIMAL LAD	2.73 (2.10-3.56)	<0.001	3.13 (1.78-5.53)	<0.001
BYPASS GRAFT	0.18 (0.05-0.66)	0.009	4.46 (1.59-12.53)	0.004
RESTENOSIS	58.65 (24.95-137.90)	<0.001	-	-
CTO	3.68 (2.57-5.26)	<0.001	-	-
LMCA	18.91 (3.53-101.19)	<0.001	7.11 (0.63-80.48)	0.11
BIFURCATION	1.67 (1.11-2.51)	0.015	3.27 (2.37-4.51)	<0.001
VESSEL DIAMETER				
≥3mm	0.20 (0.16-0.27)	<0.001	0.21 (0.18-0.25)	0.002
LESION LENGTH				
≥30mm	4.00 (3.15-5.08)	<0.001	5.73 (3.44-9.54)	<0.001
PROCEDURE				
TWO LESIONS, SINGLE VESSEL	1.69 (1.38-3.56)	<0.001	2.23 (1.77-2.81)	<0.001
TWO VESSEL PCI	2.51 (2.06-3.07)	<0.001	2.06 (1.57-2.71)	<0.001
THREE VESSEL PCI	3.41 (2.03-5.08)	<0.001	-	

*Odds ratios are referent to stable angina (clinical indication), non-diabetic, native vessel PCI (lesion type), vessel diameter <3mm, lesion length <30mm, and single lesion procedure

5.6.3.1. Under and overuse of DES

When compared with the consensus criteria, under and overuse of DES can be identified. Table 21 compares the actual stent received with the expected stent on the basis of the consensus criteria. In the majority of lesions, 3,761 (58.8%), DES and BMS were used for the expected indications. In 545 (17.0%) lesions treated with a DES, BMS use was predicted (i.e. DES were “overused” for these inappropriate indications). 705 (22.1%) lesions were treated with a BMS, when DES use was predicted (i.e DES were “underused” for appropriate indications).

Table 22 outlines the rates of predicted and actual DES use by hospital. These data apply to a different time period to that described in chapter 3, but nonetheless crude differences in DES use between hospitals are seen (range 26 to 66%). Predicted DES use varied from 31 to 54% due to case mix differences, although the rates of expected and actual use did not directly correlate. Predicted rates of uncertain indications were between 20 and 27% of lesions. Underuse of DES occurred in every hospital; however there was a trend for lower rates of underuse in hospitals with greater overall use. Overuse also occurred in every hospital, with the converse trend evident.

Figure 19 Rate of DES use for inappropriate indications by clinical subgroup (%±95% CI)

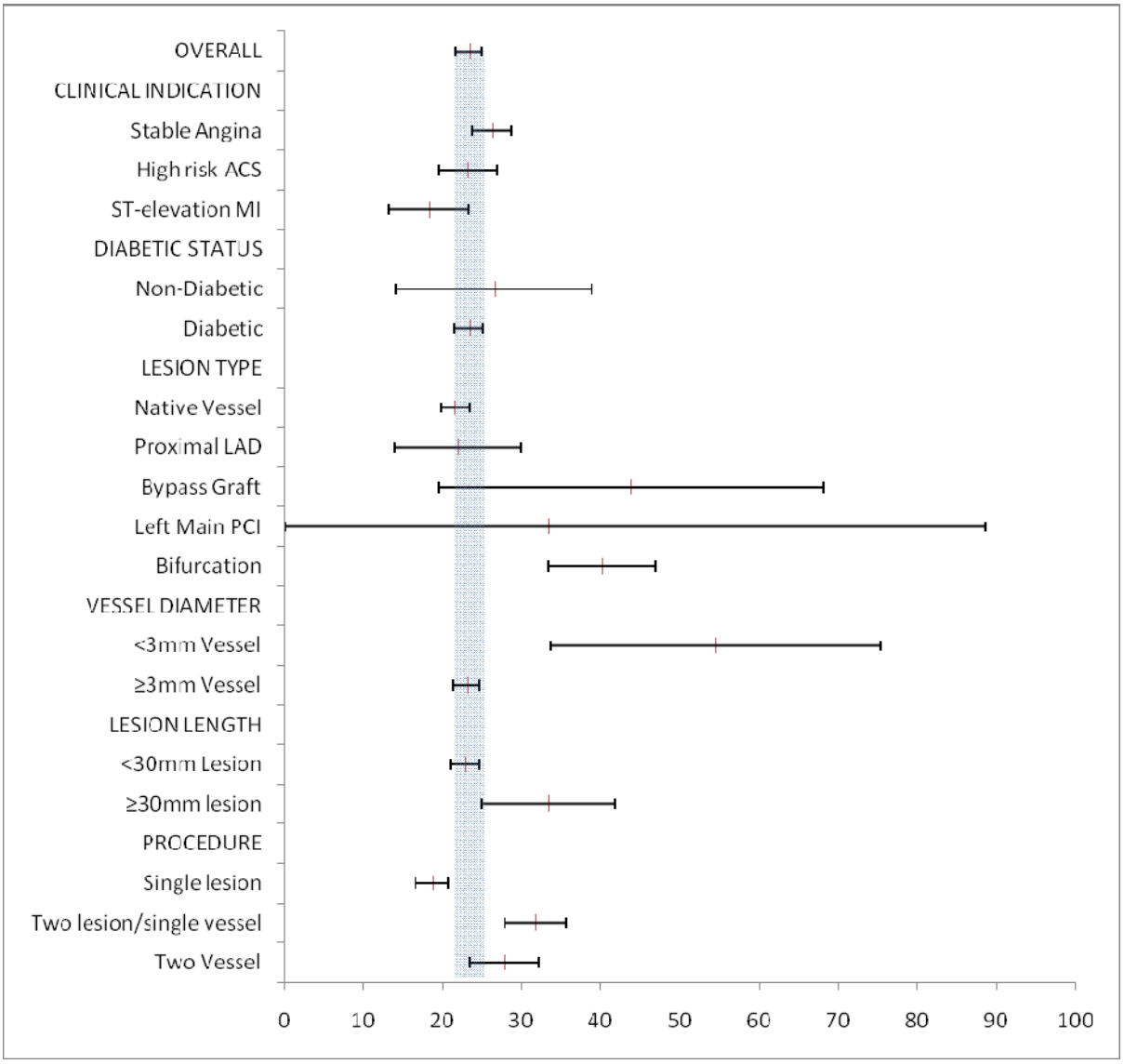


Table 21 Stent use, compared with predicted stent use

STENT RECEIVED	N	PREDICTED STENT RECEIVED	UNCERTAIN INDICATION	PREDICTED STENT NOT RECEIVED
DES	3191	1968 (61.4)	691 (21.6)	545 (17.0)
BMS	3204	1793 (56.2)	693 (21.7)	705 (22.1)
OVERALL	6395	3761 (58.8)	1384 (21.6)	1250 (19.6)

DES drug eluting stent

BMS bare metal stent

Table 22 Actual, predicted, underuse and overuse of DES by hospital

Hospital*	Predicted‡		Actual DES use (%)¶			
	DES appropriate (%)	Uncertain (%)	Overall DES use (%)	Underuse** (%)	Overuse‡‡ (%)	Uncertain¶¶ (%)
1	31	27	26	50	9	24
2	40	20	33	46	8	40
3	36	20	40	29	14	42
4	45	20	49	33	25	47
5	45	24	63	16	32	65
6	41	22	63	15	34	72
7	54	21	66	18	43	51

***Hospitals are ranked in order of actual DES use (different to the classification in chapter 3)**

‡Predicted DES use and uncertain use is calculated according to the number of appropriate lesions per hospital

¶Actual use by hospital for July 2006 - June 2007

**** Underuse is 100 – ((DES for appropriate lesions/all appropriate lesions) x100)**

‡‡ Overuse is (DES for inappropriate lesions/all inappropriate lesions)x100

¶¶ Actual DES use in uncertain indications

5.6.4. Analysis of Clinical Outcome

Finally, clinical outcome following PCI for patients with appropriate lesions treated with DES or BMS was examined. During this study period (January 2003-June 2006), 3,187 patients were treated for one or more lesions appropriate for DES. Of these patients, 1,240 were treated with a DES and 1,947 with BMS (Table 23). At baseline there were statistically significant differences between the DES and BMS groups for important covariates. Following propensity score matching, 995 pairs of patients (1,990 total patients) were included in the final analysis. Table 23 demonstrates that propensity score matching was successful in generating balanced groups with no statistically significant differences at baseline between the groups. The c-statistic for the final propensity score model was 0.71 indicating good discrimination, and the Hosmer-Lemeshow test was non-significant (P=0.86). Sensitivity analysis showed that for an unobserved variable to change the underlying conditional independence assumption for the propensity-score match, it would have to cause the odds ratio to change by 5.95. This finding implies that the propensity-score matching was very robust.

At 18 months, median follow-up was 548 days in both BMS and DES groups. During this period 83 deaths, 106 MIs and 137 TVR events occurred. Comparing BMS and DES no difference was found in the rates of death (4.1% vs 4.4%, HR 1.05, 95% CI 0.68-1.62) or MI (5.3% vs 5.5%, HR 0.97, 95% CI 0.66-1.41) (Table 24). Where DES, rather than BMS, was used to treat appropriate lesions a reduction in target vessel revascularisation at 18 months was found (8.8% vs 5.5%, HR 0.60, 95%ci 0.43-0.85) (Table 24). The absolute difference between groups was 3.3% at 18 months (number needed to treat of 30 to avoid one repeat revascularisation).

At 2 years, median follow-up was uneven between the BMS and DES group: 730 days, and 639 days respectively. Notwithstanding this discrepancy, clinical outcomes

followed a similar pattern at 2 year follow-up, suggesting no major bias had occurred. Again, no difference between DES and BMS was observed for death or MI (Table 24). A 38% relative reduction in target vessel revascularisation was seen in the DES group at 2 years, with a 3.7% absolute risk reduction (number needed to treat of 27 to avoid one repeat revascularisation).

Table 23 Appropriate indications for DES, pre- and post-matching cohorts by stent type

	Pre-matching			Post-matching		
	BMS n=1,947	***DES*** n=1,240	***p***	***BMS*** n=995	***DES*** n=995	***p***
Age (years±SD)	62.1 (10.2)	61.1 (10.7)	0.02	62±10.7	62.0±10.2	0.48
Male	1297 (66.6)	778 (62.7)	0.03	640 (64.3)	630 (63.3)	0.65
Deprivation quintile			0.11			0.27
1	335 (17.4)	239 (19.4)		185 (18.7)	185 (18.6)	
2	363 (18.8)	243 (19.7)		193 (19.4)	199 (20.0)	
3	405 (21.0)	221 (17.9)		180 (18.1)	217 (21.8)	
4	360 (18.7)	251 (20.4)		205 (20.6)	179 (18.0)	
5	465 (24.1)	279 (22.6)		231 (23.2)	215 (21.6)	
Diabetes mellitus	785 (40.3)	369 (29.8)	<0.001	317 (31.9)	309 (31.1)	0.73
Previous MI	715 (36.7)	414 (33.4)	0.06	337 (33.9)	341 (34.3)	0.88
Previous PCI	220 (11.3)	147 (11.9)	0.63	112 (11.3)	111 (11.2)	1.0
Previous CABG	172 (8.8)	108 (8.7)	0.90	87 (8.7)	88 (8.8)	1.0
Previous CVA				9 (0.9)	5 (0.5)	0.42
PVD	97 (5.0)	69 (5.6)	0.47	48 (4.8)	45 (4.5)	0.83
Chronic lung disease	139 (7.1)	93 (7.5)	0.70	71 (7.1)	74 (7.4)	0.86
Renal dysfunction	50 (2.6)	28 (2.3)	0.58	24 (2.4)	23 (2.3)	1.0
LV dysfunction	851 (43.7)	508 (41.0)	0.13	442 (42.4)	431 (43.3)	0.71
Indication for PCI			<0.001			0.64
Stable	1032 (53.0)	784 (63.2)		589 (59.2)	598 (60.1)	
Unstable angina	475 (24.4)	200 (16.1)		187 (18.8)	182 (18.3)	
NSTEMI	430 (22.1)	247 (19.9)		211 (21.2)	209 (21.0)	
STEMI	10 (0.5)	9 (0.7)		8 (0.8)	6 (0.6)	
Procedure priority			<0.001			0.51
Elective	993 (51.0)	782 (63.1)		582 (58.5)	594 (59.7)	
Urgent	901 (46.3)	421 (34.0)		382 (38.4)	374 (37.6)	
Emergency	53 (2.7)	90 (2.8)		31 (3.1)	27 (2.7)	

Table 23 cont

	Pre-matching			Post-matching		
	BMS	***DES***	***p***	***BMS***	***DES***	***p***
Lesions per procedure			0.04			0.82
One lesion	1375 (70.7)	837 (67.6)		672 (67.5)	671 (67.4)	
Two lesions	457 (23.5)	302 (24.4)		253 (25.4)	249 (25.0)	
≥ Three lesions	114 (5.9)	99 (8.0		70 (7.0)	75 (7.5)	
CAD severity			0.17			0.43
One vessel	1031 (55.6)	682 (57.0)		578 (58.0)	572 (57.6)	
Two vessel	361 (19.6)	213 (17.8)		180 (18.1)	171 (17.2)	
Two vessel (with proximal LAD)	195 (10.6)	124 (10.4)		105 (10.6)	109 (11.0)	
Three vessel/LMCA	259 (14.0)	177 (14.8)		132 (13.3)	143 (14.4)	
RVD			<0.001			0.26
≤2.5 mm	489 (25.1)	532 (42.9)		353 (35.5)	369 (37.1)	
2.6-3.0mm	1123 (57.7)	614 (49.5)		551 (55.9)	548 (55.1)	
3.1-3.5mm	245 (12.6)	86 (6.9)		85 (8.5)	72 (7.2)	
>3.5mm	90 (4.6)	8 (0.6)		6 (0.6)	6 (0.6)	
Stented length			<0.001			0.73
≤15mm	581 (29.8)	127 (21.1)		126 (12.7)	125 (12.6)	
16-30mm	956 (49.1)	607 (49.0)		535 (53.8)	529 (53.2)	
>30mm	410 (21.1)	506 (40.8)		334 (33.6)	341 (34.3)	
LMCA PCI	32 (1.6)	28 (2.3)	0.21	21 (2.1)	24 (2.4)	0.77
Bypass graft	17 (0.9)	11 (0.9)	0.97	11 (1.1)	10 (1.0)	1.0
LAD lesion	505 (25.9)	365 (29.4)	0.03	286 (28.7)	279 (28.0)	0.76
Bifurcation lesion	123 (6.3)	128 (10.3)	<0.001	87 (8.7)	91 (9.1)	0.81
CTO	228 (11.7)	153 (12.3)	0.59	121 (12.2)	122 (12.3)	0.95
Restenosis	75 (3.9)	71 (5.7)	0.01	44 (4.4)	43 (4.3)	1.0

Table 24 Clinical outcomes for propensity- score matched appropriate patients treated with BMS or DES

	BMS	DES	HR (±95%CI)	P
18 months				
Death (%)	4.1	4.4	1.05 (0.68-1.62)	0.83
Myocardial Infarction (%)	5.3	5.5	0.97 (0.66-1.41)	0.86
Target Vessel Revascularisation (%)	8.8	5.5	0.60 (0.43-0.85)	0.004
24 months				
Death (%)	5.8	5.1	1.09 (0.73-1.63)	0.68
Myocardial Infarction (%)	6.2	5.6	0.91 (0.63-1.31)	0.91
Target Vessel Revascularisation (%)	10.0	6.3	0.62 (0.44-0.86)	0.004

5.7. Discussion

It is known that DES use varies between-hospitals and between-operators in a UK healthcare setting (chapter 3). It is not clear, however, whether these variations reflect under-utilisation by some operators and hospitals or over-utilisation by others. The lack of equity in the use of DES technology has important consequences. Underuse may be detrimental to individual patients who fail to benefit, and overuse of more expensive stents could result in opportunity costs, and potentially poorer outcomes. The existence of such practice variation is at odds with the stated aim of the NHS, and raises questions regarding the applicability and relevance of current guidelines to individual patients.

Even larger variations in clinical practice exist when countries are compared. In contrast to the UK, adoption of DES in the USA was rapid with greater than 90% of lesions treated with a DES (section 3.4). This suggests, perhaps, that where no financial restrictions are placed, operators chose a DES for the majority of patients. However more recent practice data suggests some reduction in DES use within the USA, with evidence of greater selection of patients for DES. Therefore it was hitherto unclear whether operators believed DES were universally beneficial to patients, or if BMS still held some advantage in certain clinical settings. It is clearly an important issue to address, given that decisions made at patient level impact, not only on clinical outcomes, but the principle of equity of use, and overall healthcare expenditure.

5.7.1. **Appropriateness criteria and questionnaire**

In this study, an expert panel of UK interventional cardiologists and best available evidence, were used to establish appropriateness criteria for DES use. This is the first attempt to generate detailed patient and lesion level judgements for a

hypothetical set of clinical indications. These findings are more explicit than current NICE criteria[14] and could form the basis for more specific recommendations, which in turn may assist in healthcare planning and reducing inequity.

There is a strong trend for increased DES use in clinical practice with increasing levels of appropriateness. The importance of the clinical subgroups that frame the questionnaire was evident in the analysis of responses and the expected rates of DES use in clinical practice. These observations of validity support the questionnaire design and the selection of relevant clinical categories. The two-round process with controlled group feedback was successful in reducing the amount of disagreement between panellists from 8.3% to 1.9%. While some Delphi panels undergo further rounds, it is doubtful that this would have made a meaningful difference to the final judgements here.

An important finding was that many factors not included in current guidance predicted appropriateness independent of lesion length and vessel diameter criteria. These included diabetes, proximal LAD, LMCA, bifurcation, CTO and restenotic lesions (all more appropriate) and bypass graft lesions (less appropriate). Indications containing all types of clinical presentation were rated at each of the three appropriateness levels, indicating a more tailored approach may be possible. A trend, however, was noted for DES to be favoured in more stable presentations of coronary artery disease. Finally, in common with NICE recommendations, lesion length and vessel diameter were strong predictors of appropriateness rating and actual choice of stent in clinical practice.

When the modified Delphi criteria were applied to lesions encountered in clinical practice, 41.8% (±1.2) of lesions were determined to be appropriate for DES in the

12 month period analysed. In addition to these appropriate lesions, 21.6% (±1.0) of lesions were rated as uncertain, though clearly in real life an actual choice between DES and BMS would be necessary. Moreover, by using a less strict definition of "appropriate" than classically applied in a Delphi consensus study (an appropriateness score of >5), 51.7% (±1.7) of lesions would be considered appropriate for DES. During the period in question, the actual rate of DES use was 50.1% which would fall within the confidence limits of this definition.

Indeed, strictly applying NICE criteria to the 2006-7 cohort studied here would result in a similar 50.7% (±1.2) rate of DES use. It should be noted that where NICE recommend DES use, the modified Delphi panel agreed in around two-thirds of cases (68.1%). It could be argued, therefore, that employing the appropriateness ratings to guide practice may not appreciably affect current overall usage and may be acceptable on both clinical and health economic grounds.

5.7.2. **Could we target DES more effectively?**

The majority of lesions (58.8%±1.2) were treated with the "correct" stent as defined by the modified Delphi panel. A significant minority (19.6%±1.0), however, were not. When lesions appropriate for DES were analysed, the presence of a >3mm vessel or a <30mm lesion predicted BMS use, suggesting that current guidance may prevent the use of DES in patients where, the expert panel thought the benefit was highly likely. When inappropriate lesions were analysed, <3mm vessel and >30mm lesions predicted DES use in clinical practice. It seems apparent that NICE guidance, placing a strict importance on vessel and lesion dimensions, exerts an influence on practice across all the groups defined in this study.

When hospital use was analysed to determine whether differences in levels of inappropriate use explained DES practice variation, we found variation in the expected level of DES use according to the modified Delphi criteria. The "ideal" situation would be high DES use in appropriate patients and low in inappropriate patients. No hospital had this pattern of usage, suggesting that simultaneous over and underuse is occurring. Such findings suggest there is scope to better target DES.

5.7.3. **Clinical outcomes for appropriately treated patients with a DES**

Delphi studies can be criticised for a lack of external validity. So a key question is whether following such criteria results in differential clinical outcomes? Recent studies of appropriateness criteria in the use of coronary revascularisation procedures have attempted to close this loop, demonstrating that underuse of procedures such as PCI and CABG were associated with poorer clinical outcomes.[142]

In this study, an attempt was made to externally validate the ratings of our expert panel by analysing clinical outcomes for an earlier cohort of patients (January 2003-June 2006) treated with PCI. If the findings of the panel were valid, better outcomes would be expected in patients considered appropriate for DES, who received a DES. Using matched propensity scores to generate comparable groups it was found that patients who received a DES appropriately had significantly lower rates of repeat revascularisation than those who received BMS inappropriately. The absolute reduction in TVR between the groups was 3.3% at 18 months, a relative reduction of 40%; these findings are consistent with a previous large propensity-score matched study from Ontario, Canada[105] and a study of "off-label" use from our own registry (chapter 4).

Although lower rates of TVR are frequently seen in "real world" studies rather than RCTs, it is perhaps a little surprising that greater benefit was not seen in this specially selected group. Indeed, within a sub-population of diabetic patients, with small vessels (defined as <3mm) and long lesions (defined as >20mm) from the Ontario analysis, an absolute reduction of 10.2% in TVR was seen.[105] We may have expected higher overall rates of revascularisation, and greater absolute benefit with DES given the high rates of diabetes (31.5%), <3mm vessels (91.5%), >30mm lesions (33.9%) and other complex features (e.g. CTO 12.2%) in our propensity-score matched cohort. Nonetheless, net benefit from DES use was observed where our expert panel explicitly recommended it. Conversely, underuse of DES was associated with poorer clinical outcomes. Furthermore, in common with meta-analyses of RCTs, no difference in MI and death were observed between DES and BMS groups.[104]

A limitation of the current study is that the reciprocal question could not be tackled: does overuse result in poorer outcomes for DES patients? During the period January 2003-June 2006, 4,738 patients with inappropriate indications for DES underwent PCI, but only 483 were actually treated with DES. After attempting PS matching, only 378 pairs remained. Given that the main benefit from BMS in certain circumstances *may* be improved safety, the event rate (24 deaths, 55 MIs and 30 TVR) and relatively short duration of follow up was insufficient to adequately answer this question. This study is not unique in falling short of the necessary power to define the potential risks of DES, particularly in the MI population. Such a lack of data was inherent to the need to proceed with the Delphi process at the outset.

5.7.4. **Strengths and limitations of the study**

The strengths of this study include a detailed description of criteria for appropriate DES use, a large volume of contemporary data enabling a comparison between recommendations and practice, and outcome data with which to validate the

results. Nonetheless, there are limitations to the study and of this approach in general. 568 hypothetical, mutually exclusive clinical indications for PCI were included. These encompassed >99% of patients treated in the registry. However, not all the indications were represented in the study; 244 indications did not feature in the 12 months of data sampled. Panellists therefore answered a significant number of indications that did not occur, or occurred with a very low frequency, in clinical practice. Many of these redundant indications were for multi-vessel procedures. Three-vessel PCI was uncommon in clinical practice with 178 (2.7%) lesions treated in a multi-vessel procedure, but disproportionately represented in the questionnaire by 136 indications (23.9%). Nonetheless, multi-vessel PCI predicted DES use within the questionnaire and in clinical practice. Furthermore, it was possible to discern a trend whereby increasing the number of vessels, increased the appropriateness rating for receiving a DES. This is an important observation, and one that can only be made by accepting a degree of redundancy within the questionnaire to maintain an internal consistency.

The questionnaire design could be criticised for not including more lesion length options. In particular, an additional length field for 16-30mm lesions could have been included to add more texture to the opinion of the panel and allow a more direct comparison with the NICE guideline. At the time of constructing the questionnaire, the main focus within the published literature was “on-label” and “off-label” DES use. These were shorthand terms used by the US FDA to describe patients who would fall within the criteria for inclusion in the pivotal trials. Such a boundary is important as it represents a level where published evidence is not directly applicable to patients, and clinicians in actual practice extrapolate to form decisions. For lesion length, “off-label” use is generally accepted as a lesion that requires more than one stent (greater than 30mm). This level was therefore considered to be the most logical cut-point. Furthermore, the addition of a further field would have increased the total number of indications to 852. While theoretically there is no absolute maximum number of indications for a Delphi

questionnaire, more indications may result in panellist fatigue, or affect participation in the process. Nonetheless, the inclusion of only a binary "lesion length" field could be seen as a limitation.

Ideally a group meeting should have been held for round 2 – this is recommended by the UCLA/RAND Corporation. Due to logistical difficulties (panellist availability, time and study finance) this was not undertaken. I used email communication to clarify conceptual questions with respect to the questionnaire and panellist comments on decisions were circulated after round 1. The level of disagreement between panellists was 8.2% after round one, reducing to 1.9% after the second round suggesting improved consensus following round 2 (without a panel meeting).

While the purpose of the study was to generate detailed criteria for DES use, it is accepted that clinical practice is frequently more complex: even with a high level of detail, the Delphi process cannot exactly replicate real life. In addition, certain assumptions made in the questionnaire may not hold true in clinical practice, for example the assumption of average patient compliance with medications and the absence of contraindications to 12 month dual anti-platelet therapy. Such judgments in clinical practice are a necessary art, and will inevitably affect practice, but are difficult to capture within the questionnaire and even more so from abstracted data. Thus where hypothetical indications have been compared to abstracted data based on actual practice, this outcome is presented as an indication only.

One of the main advantages of the Delphi process is that it can accrue detailed judgements on a wide range of indications quicker than specially designed studies can be performed and disseminated. However in the field of DES safety and efficacy, the speed and volume of publication is so rapid that even some of the judgements

made as recently as last year could be considered out-of-date. Nevertheless, this situation faces every cardiologist when attempting to translate published research to everyday practice. This study has attempted to formalise the process to aid decision-making.

Finally, as with all observational studies outcomes are presented with the caveat that residual bias and confounding may affect the results presented. The data are not specifically collected for such analyses. Nevertheless, an accurate reflection of clinical practice has been presented, case ascertainment is high and outcomes are comprehensive, relevant and without reporting bias with respect to stent type. Furthermore, the technique of propensity-score matching explicitly presents the balancing of covariates and therefore reduces known bias.

5.8. Conclusion

A novel modified Delphi questionnaire was employed to develop detailed consensus criteria for DES use. These expert judgements were used to define levels of appropriate use and were compared to clinical practice. The results suggest that the current level of DES usage is acceptable, but could be targeted to more appropriate lesions and patients with the aim of reducing known inequities, and maximising clinical benefit from this technology. Finally, underuse of DES in appropriate patients was associated with higher levels of target vessel revascularisation.

6. Final conclusion

In chapter 3 clinical use of DES was analyzed and practice variations were found at operator and hospital level within Scotland. Furthermore, variations in international adoption and use of DES were evident when four international registries were studied. Such findings were surprising and seemed to contradict the aims of evidence-based medicine. Reductions in use were observed during 2006, a finding that is commonly taken to be a consequence of the late stent thrombosis controversy. However, the observations of variations in practice were evident both before and after this controversy.

Influences on stent choice in the "real world" were thought to be multi-factorial; on an international level, macro-economic forces exerting their influence through healthcare system regulation, payment systems, level of funding and central control are particularly important. It is also clear from the multilevel study of UK practice, however, that a clinical consensus does not exist. Current clinical guidelines do not reflect the complexities faced in clinical practice, nor are they sufficiently detailed to assist the calculation of risk and benefit for individual patients.

While it is widely accepted that the "gold standard" for assessing a treatment is through RCTs, properly conducted observational studies can also play an important role. In chapter 4, data were examined for a sub-group of patients that had been largely excluded from RCTs, therefore for whom the risks and benefits of treatment with DES were poorly defined. Findings indicated that death was lower among DES patients at 24 months, and no difference was seen in the rates of MI between matched BMS and DES cohorts. A contemporary control group was drawn on to maximise the advantages of this type of analysis, and propensity score matching was employed to minimise bias and to provide the most accurate estimate of treatment

effect. The largely reassuring findings of this study should be seen in the context of a subsequent growing body of literature also suggesting similar risks for DES and BMS when compared for both on-label and off-label use. Although the benefits of DES were evident, the absolute reduction in TVR was lower than previously demonstrated in RCTs.

Chapter 5 aimed to tackle the issue of observed practice variation due to clinical uncertainty. It was not clear whether in any given setting there had been either underuse - potentially forfeiting the benefits of DES, or overuse - where benefits may be outweighed by risks. A modified Delphi method was employed to attempt to define criteria for appropriate DES use. The modified Delphi method allows the current evidence base to be combined with pooled expert judgement in the development of best practice. Once the detailed criteria for DES use had been established, they were extrapolated to clinical practice.

It was concluded that current overall rates of DES use are acceptable. Better targeting of DES to the most appropriate lesions may be possible with the aims of reducing the known geographical inequities and maximising clinical benefit. Finally, using similar methods to chapter 4, it was shown that underuse of DES in appropriate patients was associated with higher levels of target vessel revascularisation without any difference in MI or death.

Recommendations for further work

Several areas of enquiry covered in this thesis could be developed further.

Firstly, the body of RCT evidence should be extended to include populations that

better reflect contemporary PCI practice. Such a study would compare DES with contemporary BMS in populations such as NSTEMI, multi-vessel procedures and patients with complex lesions. Such a RCT should be powered for safety endpoints, and include only clinical follow up.

Secondly, observational studies of unselected cases should be performed with extended follow up to define the natural history of late stent thrombosis and to provide interim safety data.

Thirdly, new drug-eluting stents should be subjected to the same level of scrutiny and long term follow up as the originally licensed devices (head-to-head trials are underway).

Finally, modified Delphi studies could be used to develop clinical decision aids applicable at patient level. To prove the validity of such an approach, it would be necessary to show that overuse of DES in patients defined as inappropriate was associated with no benefit or increased risk. Currently it is not clear that defining such a sub-group is possible.

7 Outputs

There are outcomes of personal benefit from an extended, dedicated period of post-graduate research that I would like to acknowledge. In common with most research degrees, this one has provided excellent opportunities to develop organisational skills, critical appraisal, and scientific writing for publication. Such skills are among the most transferable and complementary both to my future career in clinical cardiology and further research projects.

In September 06, a month after the start of this MD, the stent thrombosis controversy placed the subject of this thesis at the "cutting edge" of clinical cardiology research. This was a "double-edged sword", as the comprehensive literature review I had prepared became rapidly out-of-date with the availability of new data (much of which was only in abstract form initially). The experience of keeping up-to-date in the single topic of drug-eluting stents brought with it an intensity of study and a need to be flexible with the exact content of the final work. Also, to ensure my work remained relevant to a wider audience I needed to submit manuscripts and abstracts for publication throughout the period of study. Balancing the multiple strands of this MD degree was therefore a logistical challenge.

Due to the additional questions that arose, the study scope broadened to include the "off label" outcome study (presented in Chapter 4). This was published in the first edition of *Circulation: Cardiovascular Interventions* and presented at the ESC (Munich 2008) and TCT (Washington 2008), thus contributing to the "DES safety debate". By preparing the "off-label" study I gained insights in to the importance of data analysis and critical appraisal of your own work (the final study had been through several iterations). The process of peer review for this, and other studies, lays bare the limitations of all research methods. An understanding of such

limitations is a strength of any piece of research. Where possible I have tried to outline the inherent limitations of any of my chosen techniques.

The development of skills in handling large databases, data analysis and knowledge of epidemiological and statistical methodologies have been significant outcomes for me, along with the acquisition of considerable expertise in database and statistical packages, such as Excel, SPSS and MLWin. A large number of these skills have been developed by wide reading of statistical and epidemiological reference texts and consulting statistical journals (for example, Statistics in Medicine Journal and Statistical Primer for Cardiovascular Research series in *Circulation*). But for the more advanced techniques I have had the inestimable benefit of effective collaboration by being able to consult directly with statisticians, namely Alex McConnachie and Daniel MacKay at the University of Glasgow

A further invaluable experience was in the collaboration with international researchers, which was ultimately fruitful, both as a paper published in the American Heart Journal in 2009 and in the development of my modified Delphi study. To facilitate the international DES comparison, I liaised with US, Canadian and Belgian colleagues and co-ordinated the collation and formatting of the data, and its analysis, interpretation and write-up. Although time consuming and at times a technically difficult exercise dealing with the idiosyncrasies of relatively disparate datasets and health care systems. The success of this paper will hopefully herald further collaborations with the international research centres involved.

I was fortunate to have Prof Jill Pell and Dr Keith Oldroyd as my research supervisors. Individually they have great experience, expertise and are extensively published in their respective fields of cardiovascular epidemiology and

interventional cardiology. Throughout this process I have liaised regularly with both; such direct contact with international experts is clearly of great benefit in its own right. I have also benefitted from their contacts and been provided with outstanding academic opportunities such as attending international conferences, and working with other researchers at both the BHF Cardiovascular Research Centre and the Section of Public Health and Health Policy at the University of Glasgow. The appropriate guidance of Prof Pell and Dr Oldroyd, have left me with "ownership" over the management, direction and ultimate content of my studies.

Finally, I am pleased to have had several papers accepted for peer review journals and to have presented the research at national and international cardiovascular conferences. Output from this thesis are listed below.

ORIGINAL ARTICLES

Austin D, Oldroyd KG, Holmes DR Jr, Rihal CS, Galbraith PD, Ghali WA, Legrand V, Taeymans Y, McConnachie A, Jill P Pell on behalf of the APPROACH Investigators, Belgian Working Group on Invasive Cardiology, Mayo Clinic PCI Registry, and Scottish Coronary Revascularisation Registry. Drug-eluting stents: a study of international practice. *Am Heart J* 2009; 158:576-584

Austin D, Oldroyd KG, McConnachie A, Slack R, Eteiba H, Flapan AD, Jennings KP, Northcote RJ, Pell ACH, Starkey IR, Pell JP. Drug-eluting stents versus bare-metal stents for "off-label" indications: a propensity score matched outcome study. *Circulation: Cardiovascular Interventions* 2008;1:45-52

Austin D, Oldroyd KG, McConnachie A, Slack R, Eteiba H, Flapan AD, Jennings KP, Northcote RJ, Pell ACH, Starkey IR, Pell JP. Hospital and operator variations in drug-eluting stent use: a multi-level analysis of 5967 consecutive patients in Scotland. *J Public Health (Oxf)* 2008; 30:186-193.

REVIEW/EDITORIAL

Austin D, Oldroyd KG, Pell JP. Observational studies and drug-eluting stents – some are more equal than others. *EuroIntervention* 2009; 4; 419,421, 423

Austin D, Pell JP, Oldroyd KG. Drug-eluting stents: a review of current evidence on clinical effectiveness and late complications. *Scot Med J* 2008; 53:16-24.

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LETTERS

Austin D, Pell JP, Oldroyd KG. Bare-metal versus drug-eluting coronary stents. *N Engl J Med* 2008; 358:2516-2518.

Austin D, Pell JP, Oldroyd KG. The rise and fall of drug-eluting stents: time trend analysis in 13,647 consecutive patients undergoing percutaneous coronary intervention. *Am Heart J* 2007; 154:e37.

ABSTRACTS

Oral

Austin D, Oldroyd KG, McConnachie A, Slack R, Eteiba H, Flapan AD, Jennings KP, Northcote RJ, Pell ACH, Starkey IR, Pell JP. Drug-eluting stents versus bare-metal stents for "off-label" indications: a propensity score matched outcome study. European Society of Cardiology (Munich), August 2009 and Transcatheter Theraputics (Washington), October 2009.

Austin D, Oldroyd KG, McConnachie A, Slack R, Eteiba H, Flapan AD, Jennings KP, Northcote RJ, Pell ACH, Starkey IR, Pell JP. "Off-label" and untested indications for drug-eluting stents. Scottish Cardiac Society, September 2007

Posters

Austin D, Oldroyd KG, Holmes DR Jr, Rihal CS, Galbraith PD, Ghali WA, Legrand V, Taeymans Y, McConnachie A, Pell JP. Drug-eluting stents: a study of international practice. Moderated poster, British Cardiovascular Society (2009).

PRIZE

Best oral presentation at Scottish Cardiac Society (2008)

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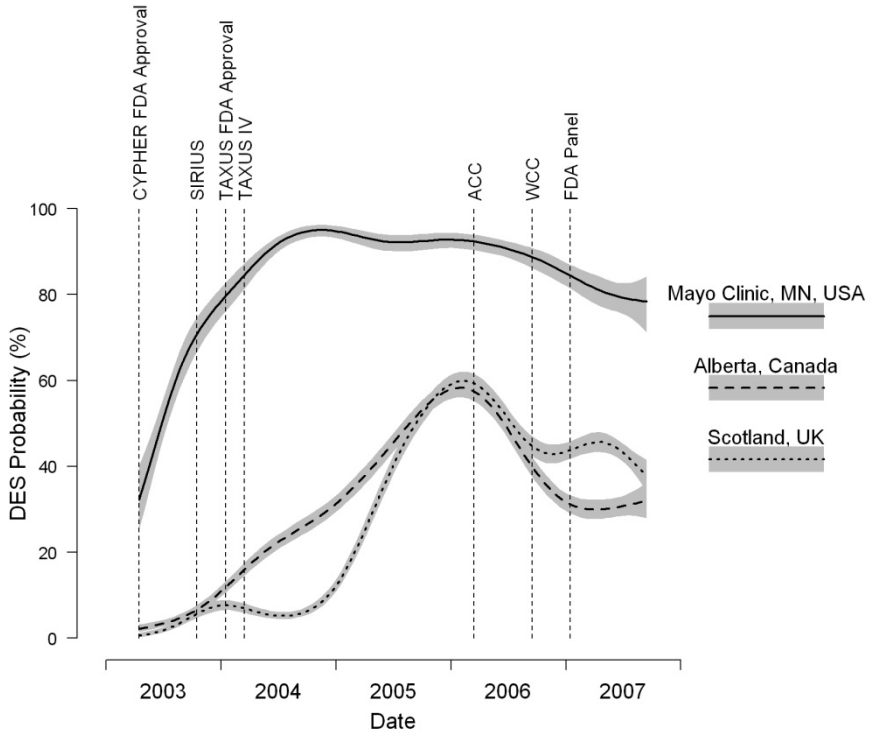
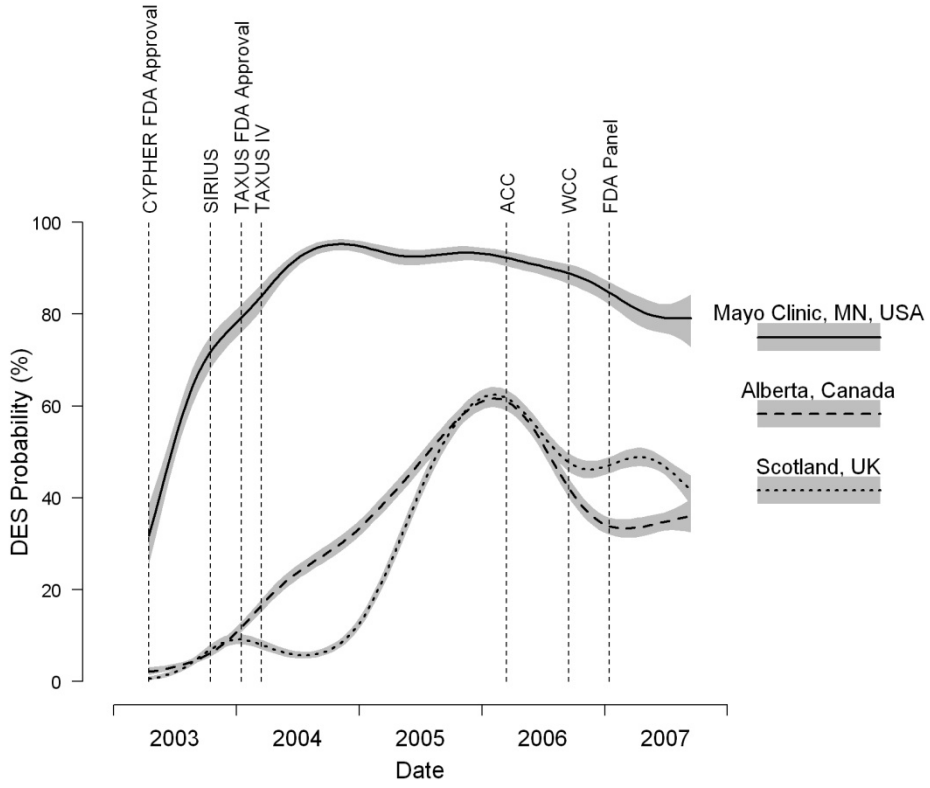
Appendix I. Alternative figures showing single lesion (randomly selected) per procedure (above) and all lesions included in the analysis (below).





Appendix II. Letter of Invitation to panellists

BHF Cardiovascular Research Centre
University of Glasgow
126 University Place
Glasgow
G12 8TA
Tel: 0141 330 2567
e-mail: d.austin@clinmed.gla.ac.uk

Dear

Re: UK expert panel on the appropriate use of drug-eluting coronary stents

We are writing to invite you to participate in an expert panel of Interventional Cardiologists from across the UK. Our aim is to use Delphi methodology to develop criteria for the appropriate use of drug-eluting stents (DES) during percutaneous coronary intervention (PCI). The Delphi method is commonly used in areas of technical expertise where there is clinical controversy and evidence is contradictory; such a situation currently exists with regard to stent selection during PCI.

Your participation in the process would involve the completion of a questionnaire rating the appropriateness of DES use for a comprehensive list of indications for PCI. The questionnaire is necessarily detailed and would take approximately three hours to complete. You would be asked to complete the questionnaire on two separate occasions. The second occasion will include feedback from other panellists from the first round (this is integral to the Delphi method).

We would be grateful if you would reply to this invitation, indicating whether or not you wish to participate. Should you not wish to participate, we would appreciate your nomination of another individual from your institution who would be willing to be contacted.

Many thanks.

Yours sincerely,

David Austin
Clinical Research Fellow in Cardiology, University of Glasgow

Jill P Pell
Professor of Cardiovascular Epidemiology, University of Glasgow

Keith G Oldroyd
Consultant Interventional Cardiology, Western Infirmary, Glasgow