# ORIGINAL ARTICLES

## Drug-Eluting Stents: A Review of Current Evidence on Clinical Effectiveness and Late Complications

*D Austin,[1] JP Pell,[2] KG Oldroyd[3]*

[1]Clinical Research Fellow in Cardiology, Department of Public Health and Health Policy, University of Glasgow, Glasgow, UK
[2]Professor of Public Health, Department of Public Health and Health Policy, University of Glasgow, Glasgow, UK
[3]Consultant Cardiologist and Honorary Senior Lecturer, Western Infirmary, Glasgow, UK

**Correspondence to**

Dr Keith G Oldroyd
Consultant Cardiologist and Honorary Senior Lecturer, Department of Cardiology, Western Infirmary,
Dumbarton Road, Glasgow, G11 6NT UK
e-mail: keith.oldroyd@northglasgow.scot.nhs.uk Tel: +44 141 211 2441 Fax: +44 141 211 1906

**Abstract**

Drug-eluting stent (DES) use has increased greatly as a result of early trial evidence of a reduction in restenosis. However, thet are expensive and do not improve patient survival. Therefore their use has been rationed in some countries. There is a paucity of clinical evidence for some patient groups such as non-ST elevation myocardial infarction and multi-vessel disease. Recent studies suggest that the early benefits of drug-eluting stents may be offset by an increased risk in late stent thrombosis which is a potentially fatal complication. However, the absolute risk appears low and, as yet, there is no evidence of an increased risk of stent-thrombosis related myocardial infarction or death in patients studied in randomised clinical trials. Long-term use of anti-platelet therapy may protect against the risk of late stent thrombosis but the optimal treatment strategy is currently unclear. The aim of this paper is to provide an up-to-date review of the current evidence on DES; including clinical effectiveness, the limitations of existing trials, the emerging evidence on late stent thrombosis and the potential role of clopidogrel.

### Introduction

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 bare metal stents (BMS) in the percutaneous treatment of coronary heart disease.[1,2] Consequently, their use has increased exponentially. However, there is no evidence that drug-eluting stents (DES) reduce the risk of death or myocardial infarction(MI). In fact, recent evidence suggests that use of DES may be associated with late stent thrombosis which, in turn, often results in myocardial infarction or death.[3,4,5] The aim of this paper is to provide an up-to-date review of the current evidence on DES; including clinical effectiveness, the limitations of existing trials and the emerging evidence on late stent thrombosis.

### Clinical Effectiveness of Drug-Eluting Stents

The main clinical indications for percutaneous coronary intervention (PCI) are chronic stable angina, ST-elevation myocardial infarction, and non-ST elevation acute coronary syndrome. These indications vary in the extent to which DES have been evaluated in randomised controlled trials (RCTs).

#### *Chronic stable angina*

Chronic stable angina accounts for 40-50% of PCI, and has been the main focus of DES trials (Table I). The original proof of concept studies, such as RAVEL (Randomised Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions), and TAXUS I and II (Paclitaxel-Eluting Stent Trials), were restricted to patients with single, short lesions in moderate diameter vessels who had a low baseline risk of restenosis.[6,7,8] RAVEL reported an angiographic restenosis rate of 26.6% using bare metal stents compared with 0% in the sirolimus-eluting stent (SES) group ($p<0.001$).[6] Similarly, in TAXUS II, the results were 20.1% and 5.1% for the bare metal and paclitaxel-eluting stent (PES) respectively ($p=0.0004$).[8]

In the subsequent pivotal trials the inclusion criteria were broadened to cover a wider range of lesions.[1,2] 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.[1] SIRIUS (Sirolimus-Coated Stent in Treatment of Patients with de Novo Coronary Artery Lesions) 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.[2] The DIABETES (Diabetes and Sirolimus-Eluting Stent) trial included only diabetic patients and again demonstrated superior results for SES compared to bare metal stenting.[9]

The smaller SES-SMART (Sirolimus-Eluting Versus Uncoated Stents for Prevention of Restenosis in Small Coronary Arteries) 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%, $p=0.002$).[10] In the SCANDSTENT (Stenting of Coronary Arteries in Non-Stress/Benestent Disease) trial, SES were superior to BMS when used for complex lesions such as bifurcation lesions and ostial disease and the PRISON II (Primary Stenting of Totally

Occluded Native Coronary Arteries II) trial demonstrated superiority when used in chronic total occlusions.[11,12] The recent RRISC (Reduction of Restenosis in Spahous Vein Grafts with Cypher Sirolimus-Eluting Stents) trial randomised patients with saphenous vein graft stenoses showing significantly lower target lesion revascularisation with SES (5.3% vs. 21.6%, p=0.047).[13] 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.[14,15]

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.[16] In 2006, Roiron et al. published a meta-analysis of 19 trials with up to 1 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.[17]

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.[18] PES were approved for lesions shorter than 28mm in vessels of between 2.5 and 3.75mm diameter.[19] 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 either BMS or coronary artery bypass grafting in vessels with more than one lesion, lesions requiring more than two stents and most importantly multi-vessel disease.

### *ST-elevation myocardial infarction*

PCI is used to achieve reperfusion and improve prognosis in patients presenting with ST-elevation myocardial infarction. Two published randomised trials have directly compared DES with BMS in the management of this group. The PASSION(Paclitaxel-Eluting Stent versus Conventional Stent in ST-Segment Elevation Myocardial Infarction) trial compared the Taxus stent against thick strut Express2 (Boston Scientific Corp.) or thin strut Liberte (Boston Scientific Corp.) bare-metal stents. At one year follow-up, there was a statistically non-significant reduction in both major adverse cardiac events (MACE) (8.8% vs. 12.8%, p=0.12), the primary end-point, and target lesion revascularisation (5.3% vs. 7.8%, p=0.31).[20] TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Angioplasty) 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).[21] 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.

### *Non-ST Elevation Acute Coronary Syndrome*

Most trials assessing DES efficacy have explicitly excluded patients with ST-elevation myocardial infarction. However, they have varied in the extent to which patients with unstable angina and non-ST elevation myocardial infarction have been included. For example, 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) and E-SIRIUS (European Sirolimus-Eluting Stent in de Novo Native Coronary Lesions) 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 myocardial infarction patients.[22,23,24] SIRIUS did include patients with Braunwald III unstable angina, however the absolute numbers were small, and troponin measurement and ST segment change were not collected at baseline.[2,25] TAXUS IV included 387 patients with unstable angina and 87 with non-ST elevation myocardial infarction, but the latter group accounted for only 6.6% of the whole study population.[1,26] The BASKET (Basel Stent Kosten-Effektivitäts 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 myocardial infarction.[27]

As yet, none of the randomised clinical trials have had sufficient power to undertake subgroup analysis in patients presenting with non-ST elevation myocardial infarction. This deficit is important since such patients account for an increasing proportion of admissions for acute coronary syndrome.

## Limitations of Drug-Eluting Stent Randomised Clinical Trials

### *Use of protocol-mandated angiography*

It has been standard practice for DES trials to use protocol-mandated angiography at between six and nine months follow up to identify angiographic restenosis. All of the trials listed in Table I 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 (Randomized Comparison of the Endeavor ABT-578 Drug Eluting Stent with a Bare Metal Stent for Coronary Revascularization) trial. 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).[28]

Secondly, there may be a systematic difference in the effect on DES and BMS. The decision to use angiography at six to nine 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.

### *Choice of bare metal stent control*

Where a RCT involves intervention in the control arm, the choice of this control 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 I). 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 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.[29,30]

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.[20] 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 MACE (7.2% vs. 12.1%, $p=0.02$), the magnitude of the difference was lower than in previous studies.[27] 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).[31] 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 recent ENDEAVOR II trial compared a zotarolimus-eluting Endeavor stent (Medtronic) 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% $p<0.0001$).[28]

## Late Complications

Stent thrombosis is uncommon, but frequently results in myocardial infarction or sudden death.[4] 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.[32] 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.[33] 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. bifurcation stenting), malapposition of the stent and the 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.

### *Meta-analyses of late outcome*

Risk of late stent thrombosis, MI, and mortality have been assessed by a number of recent meta-analyses (Table II). Three analyses aggregated data at study level, using conference presentations and published data,[34,35,36] whilst five analyses have pooled data at patient-level from original data-sources.[3,37,38,39,40]

Nordmann et al published a study-level meta-analysis of late mortality in seventeen RCTs.[36] 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%, $p=0.03$).[34] 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 risk of angiographically-confirmed stent thrombosis in a study-level meta-analysis of fourteen RCTs.[35] 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.[37] 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.[3,38-40] Stone et al. showed very late stent thrombosis (after one year) was significantly higher in the PES group.[3] 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%, $p=0.025$).[3] Analysing the same group of RCTs, Mauri et al applied new standardised definitions of stent thrombosis (Figure 1).[40] No difference in stent thrombosis was observed overall, though in common with other analyses, definite or probable thrombosis occurring after one 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.[38,39]

### *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.[41] 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 (Basel Stent Kosten Effektivitäts Trial - Late Thrombotic Events) observational study who had not experienced a MACE (death, MI or target vessel revascularisation) by 6 months.[42] 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 increased 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.

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).[43] 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 myocardial infarction were more common following DES both before and after adjustments for co-variates. Absolute event rates were low however.[44]

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 were 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).[45] 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 of only borderline statistical significance after adjustment for baseline clinical factors (adjusted HR 1.31, 95% CI 0.99-1.72).[46]

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.[2,47] There have also been disparities in the timings applied to stent thromboses. In order to address these inconsistencies, the Academic Research Consortium has proposed a new definition of definite, probable or possible stent thrombosis, with timing of events classified as early, late or very late (Figure 1).[48]

**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
   a. new acute onset of ischaemic symptoms at rest
   b. new ECG changes suggestive of acute ischaemia
   c. 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 |

***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.[49] 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 PREMIER (Prospective Registry Evaluating Myocardial Infarction Events and Recovery).[50] 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 myocardial infarction.[4] 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.[51] 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.

In October 2006, the British Cardiovascular Intervention Society reported that the current consensus was to maintain clopidogrel therapy for at least one year, and indefinitely in certain patients at higher risk of thrombosis.[52] The Food and Drug Administration in the United States initially recommended clopidogrel therapy for three and six months following SES and PES insertion respectively.[18,19] After a recent advisory hearing, the FDA suggested 12 months clopidogrel therapy for those patients at low risk of bleeding.[53]

## Conclusion

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 myocardial infarction 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 use 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 myocardial infarction, 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 myocardial infarction 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.

## Conflicts of interest

Dr D Austin and Prof JP Pell have received research funding from Boston Scientific. Dr KG Oldroyd has received speaker and consultancy fees from Boston Scientific, Medtronic and Cordis J&J.

**Table I.** Randomised controlled trials of 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[6] | 238 | Bx Velocity* | Single lesion, native vessel, D 2.5-3.5mm, L <18mm | Multivessel, CTO, LMS, ostial, thrombus, bifurcation |
| SIRIUS[2] | 1,058 | Bx Velocity* | Single lesion, native vessel, L 15-30mm | Multivessel, CTO, LMS, ostial, thrombus, bifurcation |
| E-SIRIUS[23] | 352 | Bx Velocity* | Single lesion, native vessel, D 2.5-3.0mm, L15-32mm | Multivessel, CTO, LMS, ostial, thrombus, bifurcation |
| C-SIRIUS[22] | 100 | Bx Velocity* | Single lesion, native vessel, D: 2.5-3.0mm, L 15-32mm | Multivessel, CTO, LMS, ostial, thrombus, bifurcation |
| SES-SMART[10] | 257 | Bx Sonic* | Single lesion, native vessel, D: <2.75mm, L, <33mm | Calcified, thrombus, >1 lesion/artery |
| Pache et al.[31] | 500 | BeStent2** | Native vessel | LMS, instent restenosis |
| DIABETES[9] | 160 | Bx Velocity* | Single lesion, native vessel | LMS, instent restenosis |
| SCANDSTENT[11] | 332 | Bx Velocity* | Native vessel. CTO, bifurcation, ostial or angulated | LMS, thrombus |
| PRISON II[12] | 200 | Bx Velocity* | Native vessel, CTO >2 weeks | |
| RRISC[13] | 75 | Bx Velocity* | SVG, D: 2.5-4mm | Distal graft anastamotic stenosis, occluded SVG |
| **Polymeric paclitaxel-eluting stent (PES)** | | | | |
| TAXUS I[7] | 61 | NIR* | Single lesion, native vessel, D 3.0-3.5mm, L <12mm | LMS, >1 stent |
| TAXUS II[8] | 536 | NIR* | Single lesion, native vessel, D:3-3.5mm, L: <12mm | LMS, >1 stent |
| TAXUS IV[1] | 1,314 | Express* | Single lesion, native vessel, D 2.5-3.75mm, L: 10-28mm | LMS; CTO; ostial; thrombus; bifurcation |
| TAXUS V[14] | 1,156 | Express2* | Single lesion, native vessel, D 2.25–4.0mm, L 10-46mm | LMS; CTO; ostial; thrombus; bifurcation |
| TAXUS VI[15] | 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***

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

| Author | Data abstraction | DES studied | No of RCTs | Outcomes |
|---|---|---|---|---|
| Nordmann et al.[36] | Study-level | PES<br>SES | 9 PES<br>8 PES | Death, cardiac death, non-cardiac death |
| Camenzind et al.[34] | Study- level | PES<br>SES | 4 SES<br>5 PES | Q wave MI or death |
| Bavry et al.[35] | Study-level | PES<br>SES | 5 PES<br>9 SES | Protocol defined stent thrombosis |
| Holmes et al.[37] | Patient-level | SES | 4 SES | Death, cardiac death, non-cardiac death; protocol defined stent thrombosis |
| Stone et al.[3] | Patient-level | PES<br>SES | 5 PES<br>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.[38] | Patient-level | SES | 14 SES | Death; death and MI; MACE; protocol defined stent thrombosis |
| Spaulding et al.[39] | Patient-level | SES | 4 SES | Death, cardiovascular death, non-cardiovascular death; death or Q-wave MI; death or MI |
| Mauri et al.[40] | Patient-level | SES<br>PES | 4 SES<br>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*

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