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Drug-Eluting Stents in Percutaneous Coronary Intervention

A Benefit-Risk Assessment

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Abstract

Drug-eluting stent (DES) therapy has represented a very significant milestone in the evolution of percutaneous coronary intervention (PCI) therapy. This review attempts to provide a balanced overview of the unprecedented wealth of data generated on this new technology, by examining the evidence bases for anti-restenotic efficacy, safety and cost effectiveness. The performance of a DES may be related to each of its three components: stent backbone; carrier polymer (to control drug-release kinetics); and active drug. In terms of anti-restenotic efficacy, the most appropriate parameters to examine are target lesion revascularization, angiographic restenosis and late luminal loss. The principal safety parameters are overall mortality, myocardial infarction (MI) and stent thrombosis. Anti-restenotic superiority of DES over bare metal stents (BMS) has been demonstrated across a spectrum of disease

from straightforward 'vanilla lesions' through higher disease complexity in pivotal clinical trials to phase IV studies of efficacy in 'off-label' populations. The treatment effect of DES versus BMS is consistent in terms of a reduction in the need for repeat intervention of the order of 35–70%. Regarding differential efficacy of first-generation DES, a benefit may exist in favour of the Cypher® (sirolimus-eluting) stent over Taxus® (paclitaxel-eluting), particularly in high-risk lesion subsets. The second-generation approved devices are the Endeavor® (zotarolimus-eluting) and Xience™ (everolimus-eluting) DES. While all four of these stents are permanent polymer-based, the current focus of development is towards DES platforms that are devoid of durable polymer, the presence of which has been implicated in late adverse events. In terms of safety concerns raised in relation to DES therapy, it is reasonable to conclude the following at 4- to 5-year post-stent implantation: (i) that there is no increased risk of death or MI with DES (neither is there a general signal of mortality reduction with DES) compared with BMS; and (ii) there is very little, if any, overall increased risk of stent thrombosis with DES compared with BMS, although a difference in the time distribution of thrombotic events after PCI may exist, i.e. a slight excess of events with BMS in the first 6 months and with DES beyond 12 months. Duration of dual anti-platelet therapy after stenting is a central issue and is also, at present, a matter of clinical equipoise. A threshold for cost effectiveness likely exists where the price premium associated with DES is approximately €450. On the balance of benefit and risk data available, DES implantation should be the preferred approach across the spectrum of patients with obstructive coronary disease who require PCI therapy.

1. Drug-Eluting Stent (DES) Therapy: A Historical Perspective

The history of percutaneous coronary intervention (PCI) is one of serial innovation and technological and pharmacological refinement developments that have revolutionized the treatment of obstructive coronary artery disease. Andreas Grüntzig, a German radiologist[1] performed the first successful, non-operative dilatation of a coronary stenosis in clinical practice on 16 September 1977. Balloon angioplasty, it transpired, was limited in effectiveness both by a high-incidence of abrupt vessel closure after balloon dilatation and a requirement for later re-intervention in up to 30–35% of cases. A potential solution to the problem of abrupt vessel closure was the implantation of an expandable metal mesh, on a bail-out (as required) basis, in order to maintain vessel patency following balloon dilatation. The first commercially available stent was developed by Palmaz[2] and Schatz[3], while Jacques Puel is credited with the first implantation of a stent in human coronary arteries in Toulouse, France, in March 1986.[4,5] Availability of data from the European BENESTENT (Belgium and Netherlands Stent) study[6] and the US STRESS (Stent Restenosis Study)[7] in 1994 provided an evidence base for extension of their use to an elective basis, which was a development that would significantly attenuate the problem of late luminal re-narrowing (restenosis). The inherent thrombogenicity consequent on the exposure of metal stent struts to circulating blood resulted in a restrictive rate of thrombotic stent occlusion in the immediate aftermath of PCI, despite aggressive anticoagulant therapy which itself gave rise to a high rate of local access-site complications. Subsequent investigation demonstrated that a strategy based on dual antiplatelet therapy (DAT) with aspirin (acetylsalicylic acid) and a thienopyridine was significantly more

efficacious and better tolerated than anticoagulant therapy, thereby facilitating more widespread adoption of stenting into clinical practice.[8-10]

This left neo-intimal hyperplasia, a process of scar tissue formation at the site of the stented segment resulting in need for repeat intervention in up to 20% of cases, as the remaining Achilles' heel of catheter-based intervention. Drug-eluting stent (DES) therapy involves the incorporation into a supporting stent platform of anti-mitotic or immunosuppressive agents, with facilitated delayed elution targeted at inhibition of smooth muscle cell proliferation the principal component of neointimal overgrowth (figure 1). The performance of a DES is related to each of these three components: namely, the stent backbone; the carrier polymer (to control drug-release kinetics); and the active drug.[1] The European Society of Cardiology congress in 2001 saw the presentation of initial results of the RAVEL (RAndomized study with the sirolimus coated BX™ VElocity balloon expandable stent in the treatment of patients with *de novo* native coronary artery Lesions) [Cypher® stent, Cordis Corporation, Miami Lakes, FL, USA] trial, which appeared to herald the eradication of neo-intimal hyperplasia and the culmination of PCI technological development.[11] Five years later, proceedings from the annual congress of the same society provoked widespread concern with the presentation of a series of reports and debates on a potential increased risk of death and myocardial infarction (MI) associated with DES therapy.[12,13] This review will attempt to provide a balanced assessment of the benefits and risks associated with DES treatment on the basis of evidence accumulated since 2001.

2. Benefit-Risk Evaluation: Efficacy and Safety Endpoints

Over the last 15 years, many stent trials employed a composite endpoint of major adverse cardiac events (MACE) as the primary outcome

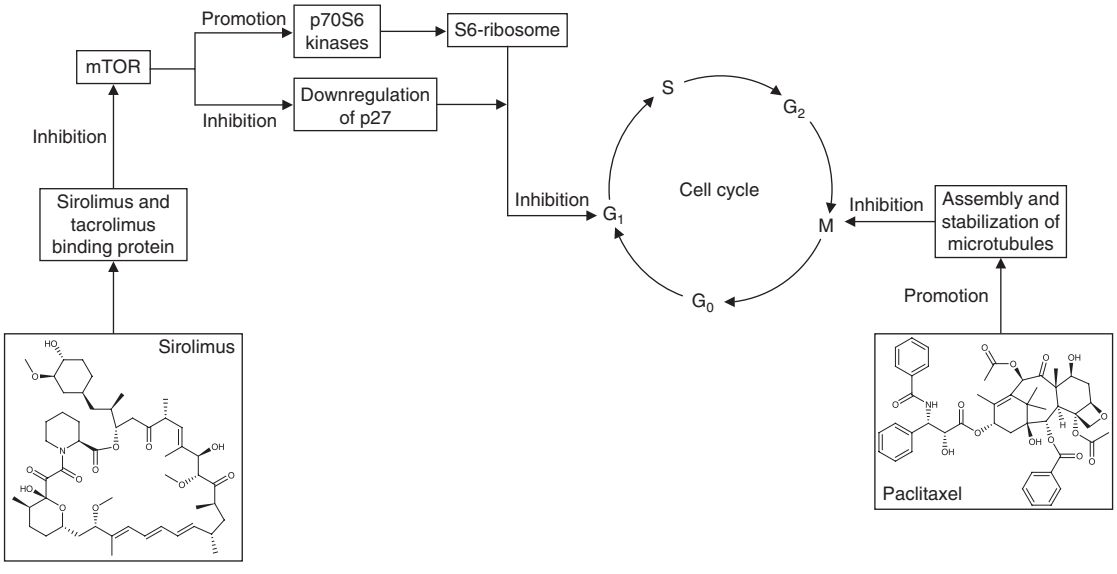


Fig. 1. Mechanism of action of drugs used on the US FDA-approved drug-eluting stent platforms. Sirolimus is the active drug in the Cypher® platform; paclitaxel in the Taxus® platform. Zotarolimus (Endeavor® stent) and everolimus (Xience™ stent) are sirolimus analogues and act via the same pathway. **mTOR** = mammalian target of rapamycin (sirolimus).

1 Proprietary stent types combine these components in a specific manner, which effects drug-elution kinetics and performance. As such, proprietary stent names are preferred over generic names in this review.

measure for sample-size determination. An endpoint such as this, which typically comprises death, MI and repeat revascularization, incorporates both efficacy and safety events and is attractive in that it reduces sample sizes and may be thought to provide an estimate of net clinical benefit. On the other hand, the result is that studies may be powered neither for efficacy nor safety outcomes.[14]

In terms of anti-restenotic efficacy, the target of DES technology is the minimization of neointimal hyperplasia. In angiographic studies, this may be quantified by examining rates of late luminal loss (defined as the difference between minimal luminal diameter post-PCI and minimal luminal diameter at surveillance angiogram) or percentage diameter stenosis at follow-up angiography. Conventionally, a percentage diameter stenosis ≥50% at follow-up is considered to represent (binary) angiographic restenosis. For reasons beyond the scope of this review, an 'in-stent' analysis is arguably more appropriate for late luminal loss, whereas an 'in-segment' analysis (in-stent + 5 mm margins proximal and distal to stent edges) is more pertinent for percentage diameter stenosis and binary angiographic restenosis. Since not all cases of binary restenosis require repeat intervention, the rate of target lesion revascularization (TLR) is the endpoint of most relevance to the clinical effectiveness of a stent platform in maintaining durable arterial patency.

Regarding safety outcomes, which are typically considerably less frequent and may occur at varying lengths of time after the index PCI, the endpoints of interest are death, MI or stent thrombosis. It should also be noted that the ascription of late adverse events as definitely stent-related (as opposed to related to disease progression) can sometimes be difficult. A conservative model involving the designation of safety endpoints as including any adverse outcome, whether specifically related to the use of the device or not, has been advocated, and standardized definitions for stent thrombosis have also been agreed upon (table I).[15] Detailed discussion is provided in the consensus document from the Academic Research Consortium (ARC) from their meeting in Dublin, Ireland, in 2006.[15]

Table I. Stent thrombosis definitions (according to Academic Research Consortium criteria)

Term	Definition
Definite stent thrombosis	Presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion
Probable stent thrombosis	Unexplained death within 30 days after the procedure or acute myocardial infarction
Possible stent thrombosis	All unexplained deaths occurring at least 30 days after the procedure
Acute stent thrombosis[a]	Occurring within 24 hours following the index PCI
Subacute stent thrombosis[a]	24 hours to 30 days following the index PCI
Late stent thrombosis	31–360 days following the index PCI
Very late stent thrombosis	After 360 days following the index PCI

a Early stent thrombosis includes patients with acute and subacute stent thrombosis (0–30 days following the index PCI).

PCI = percutaneous coronary intervention.

3. Benefit Assessment

3.1 From 'Vanilla Lesions' Through Pivotal Trials to Off-Label Use

As with many new technologies, DES implantation was first studied in stable disease with straightforward morphology; the so-called 'vanilla lesions'. These studies were designed to assess the performance of the investigational devices under ideal conditions – what might be termed device *efficacy* rather than *effectiveness*.[16] For example, the RAVEL study enrolled stable patients with single *de novo* stenoses in 2.5–3.5 mm vessels (excluding left main) that could be covered with a single 18 mm stent.[11] Patients were randomized to Cypher® or bare metal stent (BMS) implantation. The results were dramatic: the abolition of late luminal loss, and angiographic and clinical restenosis (figure 2). In particular, late loss was reduced from 0.80 to –0.01 mm, binary restenosis was reduced from 26.6% with BMS to 0% with Cypher® ($p < 0.001$) and TLR was reduced from 23.7% to 0% ($p < 0.001$). In a similarly low-risk population, comparable rates of angiographic (20.7% vs 2.3%; $p < 0.001$) and clinical restenosis (12.0% vs 4.6%; $p = 0.043$) reduction was reported with the

first commercially available paclitaxel-eluting stent (Taxus®, Boston Scientific, Natick, MA, USA) albeit with the accommodation of a small degree of late luminal loss (0.36 mm with Taxus®) [figure 2].[17] These dramatic results led to widespread initial enthusiasm for this important new technology.[18]

A more realistic assessment of the marginal efficacy benefit of DES over BMS may be gained from analysis of so-called pivotal DES trials, such as SIRIUS (Sirolimus-eluting Stent in *de novo* native coronary lesions and TAXUS IV (figure 3).[19,20] Both of these studies enrolled larger numbers of patients with more complex lesion characteristics, although the patients themselves remain relatively low risk (no acute MI; no left main stem disease). The SIRIUS trial randomized 1058 patients with *de novo* lesions 15–30 mm in length to either Cypher® or the BMS.[19] Late luminal loss was reduced from 1.00 mm with BMS to 0.17 mm with Cypher® ($p < 0.001$). Similarly, binary restenosis was reduced from 36.3% to 8.9% ($p < 0.001$) and 9-month TLR was reduced from 16.6% to 4.1% ($p < 0.001$) [figure 3]. The TAXUS IV trial enrolled 1314 patients with lesions up to 28 mm in length.[20] Investigators reported a reduction in rates of mean late loss (0.92 mm vs 0.39 mm; $p < 0.001$), angiographic restenosis (26.6% vs 7.9%; $p < 0.001$) and TLR (11.3% vs 3.0%; $p < 0.001$) with Taxus® compared with BMS (figure 3). The TAXUS V study comprised slightly higher risk patients again, allowing vessel size as small as 2.25 mm and lesion length up to 46 mm.[23] Late loss was reduced to a slightly smaller extent (from 0.90 mm to 0.49 mm; $p < 0.001$) as were binary restenosis (33.9% vs 18.9%; $p < 0.001$) and TLR (15.7 vs 8.6%; $p < 0.001$). So we can clearly see that as lesion complexity increases, the rates of restenosis increase across trials and although the clear superiority of DES is maintained, the complete eradication of restenosis has not been realized.

In the US, licensing regulations approve DES use only in lesion types in which they were tested in the pivotal DES trials. Such lesions are *de novo* lesions in native coronary vessels between 2.5 mm and 3.5–3.75 mm in diameter and <28–30 mm in length. Ostial, bifurcated and chronically occluded lesions are excluded, as are interventions in the setting of acute MI. Although regulations differ from jurisdiction to jurisdiction, these latter implantation indications have come to be regarded as off-label usage. What evidence do we have to support DES use in this large patient group who have DES implanted for such indications (see table II)? Three large registry studies have examined the outcomes of a total of 10 216

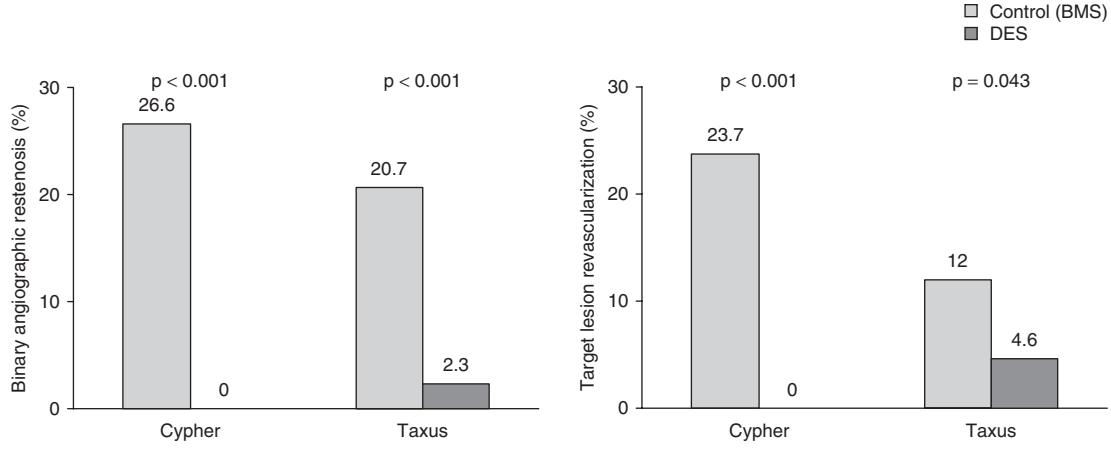


Fig. 2. Angiographic and clinical restenosis from RAVEL (RAndomized study with the sirolimus coated BX™ VElocity balloon expandable stent in the treatment of patients with *de novo* native coronary artery Lesions) [Cypher® stent][11] and Taxus II[17] trials. **BMS** = bare metal stent; **DES** = drug-eluting stent.

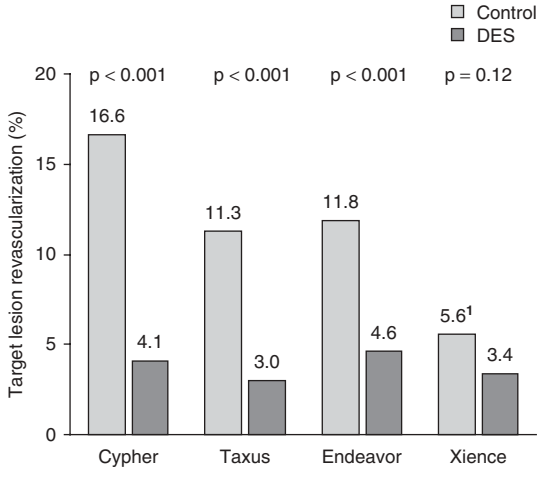


Fig. 3. Rates of target lesion revascularization at 9–12 months from pivotal trials of the four US FDA-approved DES platforms[19-22] **1** Comparator stent was also a DES (Taxus®) rather than a BMS. **BMS** = bare metal stent; **DES** = drug-eluting stent.

patients treated with off-label DES.[24-26] The conclusions may be summarized as follows: (i) off-label DES use is very common, comprising at least 50% of all interventions; (ii) off-label use patients have higher rates of death (hazard ratio [HR] ~2.0) and MI (HR ~1.5) compared with on-label use patients. This is due to increased disease and procedural complexity and seems independent of the stent type used; after adjustment for differences in patient and lesion characteristics, no significant differences between BMS and DES are observed; and (iii) the benefit of DES in reducing TLR seems to be maintained in this lesion subset after adjustment for a higher lesion complexity in the off-label groups (HR ~0.65).

3.2 The Second Generation of DES

The Endeavor® zotarolimus-eluting stent (Medtronic, Inc., Minneapolis, MN, USA) was the third stent to receive US FDA approval in October 2007. The ENDEAVOR II trial enrolled patients with a lesion length of 14–27 mm and vessel size of 2.25–3.5 mm.[21] Late loss was notably higher compared with the foregoing DES platforms (0.62 mm). Nonetheless, significantly reduced rates of binary restenosis (34.2% vs 13.3%; $p < 0.001$) and TLR (11.8% vs 4.6%; $p < 0.001$) were described for the Endeavor® stent in comparison with BMS (figure 3). In view of the already-proven efficacy superiority of Cypher® and Taxus® over BMS, next-generation stents had to prove themselves against these DES in order to meet regulatory approval thresholds. In comparison with Cypher®, Endeavor® showed significantly higher 'in-segment' late loss (0.34 mm vs 0.13 mm; $p < 0.001$).[27] The ENDEAVOR IV trial compared Endeavor® against Taxus®.[28] The primary endpoint of non-inferiority in terms of 9-month target-vessel failure was met. However, there were notable differences in both late loss (Endeavor® 0.67 mm vs Taxus® 0.42; $p < 0.001$) and binary restenosis (Endeavor® 15.3% vs Taxus® 10.4%; $p = 0.28$). The fact that this did not translate into differences in target-vessel revascularization raised the possibility that this higher degree of mean late loss might reasonably be accommodated in a patient population without a significant overspill of patients beyond the theoretical revascularization threshold.[28] In contrast with these findings, however, are the results from the recently presented SORT OUT III (Danish Organization on Randomized Trials with Clinical Outcome III) trial.[29] This all-comers trial randomized 2333 patients to either Cypher® or Endeavor® in a real-world setting, with only a small number of patients undergoing routine angiographic follow-up. They found a significantly lower rate of TLR with Cypher® compared with Endeavor® (Kaplan-Meier estimate

Table II. Off-label indications for drug-eluting stents (DES)[a]

Reference vessel <2.5 mm or >3.75 mm
Lesion length >30 mm
Restenotic lesion
Lesion in bypass graft
Left main-stem intervention
Ostial lesion
Bifurcation lesion
Chronically occluded vessel
Acute myocardial infarction

a In the US, licensing regulations approve DES use only in lesion types tested in the pivotal DES trials. Although regulations differ from jurisdiction to jurisdiction, these latter implantation indications have come to be regarded as 'off-label' usage.

HR at 9 months 6.59; 95% CI 2.57, 16.9; $p < 0.001$). One notable feature of the Endeavor® stent is a degree of enhanced deliverability. It has been observed that whereas the first wave of DES brought features that predominantly improved patient outcomes, the second generation brought features that improved operator outcomes.

The Xience™ everolimus-eluting stent (Abbott Vascular, Abbott Laboratories, Abbott Park, IL, USA; also marketed as Promus™, Boston Scientific Corporation, Natick, MA, USA) is the most recently approved DES, receiving US regulatory approval in early July 2008. SPIRIT-II (Clinical Evaluation of the XIENCE V® Everolimus Eluting Coronary Stent System) enrolled patients with reference vessels between 2.5 mm and 4.25 mm and lesion lengths up to 28 mm. Rates of late luminal loss and binary restenosis were excellent at 0.12 mm and 1.3%, respectively. The pivotal SPIRIT III trial randomized 1002 patients with similar inclusion criteria to either Xience™ or Taxus®.[22] Late loss was significantly lower with the Xience™ stent (0.16 mm vs 0.30 mm; $p = 0.002$), although Xience™ was not statistically superior to Taxus® in terms of binary restenosis (4.7% vs 8.9%; $p = 0.07$) or TLR at 12 months (3.4% vs 5.6%; $p = 0.12$) [figure 3].

3.3 The Next Generation

Concerns regarding late thrombotic events following DES implantation and the possible role of permanent polymer in this process,[30-32] have led a number of investigators to pursue development of less thrombogenic polymer-free DES models. The main challenge associated with these nascent stent technologies lies in the conservation of optimal anti-restenotic efficacy – a process strongly related to the control of release kinetics of the active drug – without resort to durable polymer.

Perhaps the largest area of innovation has been in the utilization of self-degrading biopolymer (which theoretically degrades over 3–9 months) in place of permanent polymer. The LEADERS (Limus Eluted from A Durable versus ERodable Stent coating study) investigators randomized 1707 patients to a novel biolimus-eluting stent with a biodegradable polymer or to Cypher®.[33] Late loss (0.13 mm vs 0.19 mm; $p = 0.34$), binary restenosis (6.8% vs 10.8%; $p = 0.15$) and TLR (5.4% vs 5.9%; $p = 0.62$) for the biolimus-eluting stent and Cypher®, respectively, were similar between the two platforms and non-inferiority outcomes were highly significant. Our group has also reported results from the ISAR-TEST-3 (Intracoronary Stenting and Angiographic Restenosis – Test Efficacy of Rapamycin Eluting Stents With Different Polymer Coating Strategies) study comparing the effectiveness of three different stents, all eluting sirolimus (rapamycin) and each employing a specific coating strategy to modify release of the active drug, namely a polymer-free, a biodegradable polymer and a permanent polymer (Cypher®) platform.[34] Although limitations in the sirolimus release kinetics of the polymer-free platform meant that it did not meet non-inferiority criteria against the Cypher® stent (late loss 0.47 mm vs 0.23 mm; $p_{\text{non-inferiority}} = 0.94$), the biodegradable polymer stent did prove non-inferior to the Cypher® stent (0.17 mm vs 0.23 mm; $p_{\text{non-inferiority}} < 0.001$). Rates of binary restenosis (9.0% vs 10.8%) and TLR (5.9% vs 7.9%) were also similar between the biopolymer stent and the Cypher®.

Encouraging data on a biodegradable polymer sirolimus-eluting stent has also been reported in a large registry by Chinese investigators, although randomized control trial data on the device is lacking,[35] while Costa et al.[36] have also reported maintained anti-restenotic efficacy with a low-dose sirolimus-eluting stent that is coated with self-degrading hydroxyapatite instead of polymer. Researchers have also pursued development of stents that not only have biodegradable coating but also a biodegradable stent backbone, although, in general, inferior radial strength compared with metal alloy stents has proven limiting. An exception is the ABSORB (A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions) trial which studied an everolimus-eluting DES with a biodegradable polylactic acid stent backbone and reported satisfactory anti-restenotic efficacy (late luminal loss 0.48 mm) – albeit in 'vanilla-lesion' type morphology – maintained out to 2 years.[37]

Another option is to compensate for some erosion of anti-restenotic efficacy inherent in quicker-release polymer-free devices by incorporation of a second active drug targeted at an additional element of the restenotic response cascade. Estrogen promotes stent endothelialization and may be expected to reduce neo-intimal hyperplasia. However, experience with a dual estrogen- and sirolimus-eluting platform did not result in enhanced performance efficacy.[38] Similarly, Verheye et al.[39] reported disappointing outcomes with a dual paclitaxel- and pimecrolimus-eluting stent. Probucol is a potent liposoluble antioxidant that has proven effects, both in animal models and in clinical trials, in reducing neointimal hyperplasia, the dominant cause of in-stent restenosis. We recently reported results from the ISAR-TEST-2 study comparing a probucol- plus sirolimus-eluting stent (Dual-DES) against the Cypher® and Endeavor® stents.[40] We found comparable efficacy results between the Dual-DES and the Cypher® in terms of late loss (0.23 mm vs 0.24 mm; $p = 0.78$), binary restenosis (11.0% vs 12.0%; $p = 0.68$) and TLR (6.8% vs 7.2%; $p = 0.83$). The efficacy of this Dual-DES was superior to that of the Endeavor® stent ($p < 0.01$ for all three parameters).The achievement of this very good anti-restenotic efficacy with both biodegradable polymer stents and the Dual-DES without recourse to durable polymer is an interesting development. Potential safety and/or efficacy advantages inherent in DES platforms devoid of durable polymer remain subject to further investigation and longer term surveillance.

Many other platforms are in various stages of clinical development, though an exhaustive review of this area is beyond the scope of this manuscript.

3.4 Meta-Analyses of DES versus Bare Metal Stents (BMS)

The sheer volume of trial data accumulated on DES technology over the last 8 years is overwhelming. At least sixteen meta-analyses have been published that report efficacy outcomes in DES compared with BMS. Their results are consistent in showing a clear efficacy effect in favour of DES and are summarized in table III.[41-56] The largest meta-analysis was performed by Stettler et al.[50] They identified 18 023 patients enrolled in 38 clinical trials comparing either Cypher® or Taxus® versus BMS, or Cypher® versus Taxus® in a head-to-head comparison. They used a network meta-analysis model, which allows indirect comparison between study groups across various trials. They report a reduction of 60–70% for DES against BMS in terms of need for TLR: HR 0.30 (95% CI 0.24, 0.37; $p < 0.001$) for Cypher® versus BMS and 0.40 (95% CI 0.33, 0.53; $p < 0.001$) for Taxus® versus BMS.

3.5 Limitations in Efficacy Comparison of DES against BMS

Some important caveats, outlined as follows, should be considered when interpreting efficacy comparison based on clinical trials between DES and BMS.

1. The lack of a universal BMS comparator. Initial clinical trials were typically funded by the DES manufacturer and tended to use that manufacturer's BMS. Not all BMS are equal. For example, thin-strut BMS (strut thickness ~50 μm) are associated with lower rates of late loss and restenosis compared with thicker strut stents (strut thickness ~140 μm).[57,58] A standard, thicker strut stent was invariably used by the industry in the conduct of these trials. However, our group did compare the efficacy of the commercial Cypher® against a thin-strut BMS counterpart, and noted a magnitude of benefit with the Cypher® that was in keeping with results of earlier trials.[59]

2. DES implantation is associated with a significant delay in arterial wall healing.[31] The inflammation associated with this delayed healing may drive ongoing neointimal hyperplasia late after DES implantation.[60] Consequently, DES may be subject to a degree of delayed loss of anti-restenotic efficacy that would not be seen with BMS and so a timepoint of efficacy comparison of 6–8 months, at which stage vessel healing after bare metal stenting is complete, may favour DES. In a study of 2030 patients undergoing 6–8 month and 2-year angiographic follow-up, we found a

Table III. Efficacy meta-analyses[a]

Meta-analysis (y)	Number of patients	Patient-level data included	Follow-up	Comment	Clinical efficacy assessment, TLR/TVR [HR (95% CI)]
Kirtane et al.[56] (2009)	9470	Yes	Median 2.9 y		DES v BMS: 0.45 (0.37 to 0.54; p < 0.001)
Brar et al.[55] (2009)	7352	No	7–24 mo	AMI	DES v BMS: 0.44; (0.35, 0.55; p < 0.001),
Stettler et al.[41] (2008)	14799	No	Up to 4 y	Network model	Cypher® vs BMS: 0.29 (0.22, 0.39) diabetes Taxus® vs BMS 0.38 (0.28, 0.55) diabetes Cypher® vs BMS: 0.29 (0.22, 0.38) no diabetes Taxus® vs BMS 0.46 (0.33, 0.60) no diabetes
Kumbhani et al.[42] (2008)	2951	No	6–12 mo	Diabetes only	Cypher® vs BMS 0.35 (0.27, 0.46; p < 0.001)
Gurm et al.[43] (2008)	7455	No	6–12 mo		Cypher® vs Taxus®: 0.67 (0.53, 0.84; p = 0.001)
Schömig et al.[44] (2007)	8695	Yes	9–37 mo	Inter-DES	Cypher® vs Taxus®: 0.74 (0.63, 0.87; p < 0.001)
Kastrati et al.[45] (2007)	2476	Yes	12–24 mo	AMI	DES vs BMS: 0.38 (0.29, 0.50; p < 0.001)
Boyden et al.[46] (2007)	1520	No	6–9 mo	Diabetes only	Cypher® vs BMS: 0.34 (0.26, 0.45; p < 0.001)
Pasceri et al.[47] (2007)	2357	No	8–12 mo	AMI	DES vs BMS: 0.40 (0.30, 0.54)
Stone et al.[48] (2007)	5321	Yes	2–4 y		Cypher® vs BMS: 0.29 (0.22, 0.39; p < 0.001) Taxus® vs BMS: 0.38 (0.30, 0.48; p < 0.001)
Kastrati et al.[49] (2007)	4958	Yes	12–59 mo		Cypher® vs BMS: 0.31 (0.23, 0.41)
Stettler et al.[50] (2007)	18023	No	Up to 4 y	Network model	Cypher® vs BMS: 0.30 (0.24, 0.37) Taxus® vs BMS: 0.42 (0.33, 0.53) Cypher® vs Taxus®: 0.70 (0.56, 0.84)
Schampaert et al.[51] (2006)	1510	Yes	2 y		Cypher® vs BMS: 0.25 (0.18, 0.35; p < 0.001)
Stettler et al.[52] (2006)	4513	No	8–24 mo	Diabetes No diabetes	Cypher® vs Taxus®: 0.86 (0.40, 1.86; p = 0.71) Cypher® vs Taxus®: 0.54 (0.30, 0.99; p = 0.045)
Roiron et al.[53] (2006)	8987	No	12 mo		DES vs BMS: 0.36 (0.31, 0.41; p < 0.001)
Kastrati et al.[54] (2005)	3669	No	6–13 mo	Inter-DES	Cypher® vs Taxus®: 0.64 (0.49, 0.84; 0 = 0.001)

a Meta-analyses of DES vs BMS or Cypher® vs Taxus®, reporting TLR/TVR as a primary efficacy endpoint.

AMI = acute myocardial infarction; **BMS** = bare metal stents; **DES** = drug-eluting stents; **HR** = hazard ratio; **TLR** = target lesion revascularization; **TVR** = target vessel revascularization.

mean delayed late loss of 0.12 mm between 6–8 months and 2 years, which was in marked contrast to observations in the BMS era where late loss did not tend to occur beyond 6–8 months.[61] This phenomenon may possibly be related to the presence of permanent polymer in DES designs because continuing delayed late loss was not seen with a polymer-free DES. Nonetheless, superiority of clinical restenosis rates with DES over BMS seems to be well maintained out to 4–5 years.[48,49]

3. Protocol-mandated angiographic follow-up may exaggerate the difference between DES and BMS by inflating rates of TLR.[62] However, although the existence of a TLR inflation phenomenon is clear, its corollary that this necessarily distorts the comparative efficacy of devices is not necessarily so. When well conducted randomized trials test devices under a prespecified set of conditions (including mandated angiographic follow-up), the relative magnitude of the observed treatment effect may be expected to be real, although the absolute effect may be magnified.[63,64]

4. Inter-DES Efficacy Comparison

As can be seen from the efficacy data presented earlier, there appear to be some differences in the absolute suppression of neointimal hyperplasia – as measured by the extent of mean

late loss – between competing DES platforms. Whether or not this leads to relevant differences in clinical outcomes has been the subject of much discussion and not inconsiderable investigational resources. The bulk of the inter-DES efficacy data refer to comparisons between Cypher® and Taxus®, in particular that a potential efficacy differential may exist in favour of Cypher®.[63]

As the efficacy of DES devices in preventing restenosis is typically high, discerning a performance difference between platforms can be challenging. There are three approaches that may be employed in addressing this issue, and these will be discussed in the following three subsections.

4.1 Recruit a Large Study Population Powered to Detect Differences in Clinical Efficacy Endpoints

The SIRTAX (Sirolimus-Eluting Stent Compared with Paclitaxel-Eluting Stent for Coronary Revascularization) trial randomized 1012 patients to Cypher® or Taxus® powered to detect a difference in a composite efficacy and safety (MACE) endpoint.[65] They found lower rates of MACE (6.2% vs 10.8%; p = 0.009), late loss (0.12 mm vs 0.21 mm; p < 0.001), binary restenosis (6.6% vs 11.7%; p = 0.02) and TLR (4.8% vs 8.3%; p = 0.03) with Cypher® compared with Taxus, respectively. On the other hand, Galløe and colleagues[66] recruited 2098 patients in a well designed randomized trial comparing Cypher® and Taxus® (SORT OUT II trial) in a real-world setting where only a very small proportion of patients were selected for angiographic follow-up. They found no difference in the primary endpoint of death, MI or TLR (Cypher® 98 [9.3%] vs Taxus® 114 [11.2%]; p = 0.63). Specifically, in terms of dedicated efficacy endpoints, the TLR rate was 4.5% for Cypher® versus 5.9% for Taxus® (HR 0.75; 95% CI 0.52, 1.10; p = 0.14). However, because of a lower than expected event rate, a significantly larger population would have been required to detect a difference in the primary endpoint (planned power 80%; actual power 28.7%). On the other hand, data from the SORT OUT III trial (n = 2333) comparing Cypher® with Endeavor® did demonstrate an efficacy superiority in favour of the Cypher® trial (as discussed earlier).[29]

4.2 Utilize a Surrogate Endpoint

Significant data exist concerning the reliable correlation of late luminal loss and binary angiographic restenosis as determined at follow-up angiography with clinical restenosis events (TLR).[67] The REALITY trial investigators randomized 1386 patients using a primary endpoint of angiographic restenosis.[68] They found no difference between Cypher® and Taxus® (9.6% vs 11.1%; relative risk [RR] 0.84; 95% CI 0.61, 1.17; p = 0.31). This may have been due to a relatively low-risk lesion complexity. In contrast with these findings, in ISAR (In-Stent Angiographic Restenosis)-DIABETES, 250 patients were randomized to Cypher® or Taxus® and lower rates of late loss (0.19 mm vs 0.43 mm; p < 0.001) and binary restenosis (6.9% vs 16.5%; p = 0.03) with Cypher® were found.[69] Similarly, in the high-risk lesion subset of in-stent restenosis[70] and small vessels,[71] we demonstrated an anti-restenotic superiority of the Cypher® stent over the Taxus® stent. Therefore, specifically in patients with high-risk patient or lesion characteristics, the Cypher® stent may have an edge in terms of anti-restenotic efficacy. We have already seen that the ENDEAVOR III[27] and SPIRIT III[22] trials showed superiority of Cypher® over Endeavor® and Xience™ over Taxus®, respectively, on primary angiographic endpoints.

4.3 Perform a Meta-Analysis of Available Data

We performed a dedicated meta-analysis of 16 trials comparing Cypher® with Taxus® including follow-up for 9–37 months. In terms of the primary efficacy endpoint of the need for TLR, Cypher® showed superiority to Taxus® (HR 0.74; 95% CI 0.63, 0.87; p < 0.001).[44] The meta analysis of Stettler et al.[50] reported a similar treatment effect in favour of Cypher® (HR 0.70; 95% CI 0.56, 0.84; p = 0.002). They used a network meta-analysis model for comparisons between Cypher® and Taxus®; in terms of inter-DES analysis, this involves reliance on strong assumptions about the comparability of the data.[72,73]

5. Risk Assessment

5.1 Cause for Concern?

There have been safety concerns regarding a possible increased risk of late thrombotic occlusion following DES implantation since early in the course of their utilization in routine clinical practice. McFadden et al.,[74] in Rotterdam, the Netherlands, first reported a small case series of four patients who each experienced very late (>1-year post-PCI) stent thrombosis after discontinuation of anti-platelet therapy. Subsequently, a number of studies raised concerns regarding the association of DES with stent thrombosis.[75,76] Risk factors identified in the study by Iakovou et al.[75] included (in order of decreasing importance) premature discontinuation of DAT, renal failure, bifurcation interventions, diabetes mellitus and decreased ejection fraction. The proposed mechanism for such an increased risk is delayed healing of the stented segment. Pathological studies have found evidence of ongoing vessel wall inflammation and poor stent strut endothelialization at timepoints beyond 1 year after PCI.[31] Although delayed healing is likely of multifactorial aetiology, persistent inflammatory response to the polymer residue that remains in the coronary milieu after the active drug-elution may play an important role.[32,77]

In contrast to efficacy data, which are based on a wealth of appropriately powered randomized control trials, no such study exists regarding less frequently occurring safety events. What information we have is derived predominantly from registry data and meta-analyses. Safety concerns came to the attention of the wider medical community following data presented at the World Congress of Cardiology in Barcelona in 2006. In particular, a review from Camenzind et al.[12] suggested a statistically significant increase (2.4%) in the rate of death or MI with DES compared with BMS. In addition, data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) [n = 19771] provided cause for alarm by suggesting a possible excess mortality at 3 years with DES compared with BMS treatment.[78] Prior to 6 months, they noted a slight excess of MI with BMS (excess 13.4 events per 1000 patients per year). This is a trend often noted in comparative DES versus BMS studies in the first 6 months. It may be a signal that the recommended duration of DAT following BMS implantation (i.e. 1 month) is too short. Of greater impact was the finding that beyond 6 months, a higher rate of stent thrombosis was observed with DES (excess 12.7 events per 1000 patients per year; adjusted RR 1.20; 95% CI 1.05, 1.37) and a higher mortality rate at 3 years (adjusted RR 1.18; 95% CI 1.04, 1.35). The data are somewhat limited because they were analysed prior to the adoption of universal ARC criteria for stent thrombosis. More importantly, a subsequent extension of analysis out to 4 years, found that these differences were no longer observed.[79] Nevertheless, these results gave rise to a profusion of studies examining safety outcomes following DES implantation and, among other measures, prompted the convening of a dedicated European Society of Cardiology forum on DES.[80]

5.2 Meta-Analysis Data

A summary of meta-analyses examining overall mortality as a safety endpoint in DES versus BMS randomized trials is shown in table IV.[13,41-45,47-51,53-56,81,82]

Our group undertook a meta-analysis of 14 trials with 4958 patients comparing the outcomes of patients treated with Cypher® stents and BMS.[49] We found no excess risk of stent thrombosis over 5 years (HR 1.09; 95% CI 0.64, 1.86; figure 4). However, restricting analysis to events occurring only after 1 year, there was a slight excess of events with the Cypher® stent compared with BMS (0.6% [95% CI 0.5, 1.5] vs 0.05% [95% CI 0.01, 0.4]; p = 0.02).[49] In agreement with this, a pooled analysis of data from four trials[11,19,83,84] found no evidence of an increased mortality risk with DES compared with BMS (HR 1.24; 95% CI 0.84, 1.23; p = 0.008). Of interest, however, was a signal of increased mortality in patients with diabetes (HR 2.9; 95% CI 1.38, 6.10).[81] Similarly, meta-analysis of data by Mauri et al.[85] was notable in applying ARC criteria in adjudication of stent thrombosis and

Table IV. Safety meta-analyses[a]

Meta-analysis (y)	Number of patients	Patient-level data included	Follow-up	Comment	Safety assessment, total mortality [OR (95% CI)]
Kirtane et al.[56] (2009)	9470	Yes	Median 2.9 y		DES v BMS: 0.97; (0.81, 1.15; p = 0.72)
Brar et al.[55] (2009)	7352	No	7–24 mo	AMI	DES v BMS: RR: 0.89; (0.70, 1.14; p = 0.36),
Stettler et al.[41] (2008)	14799	No	Up to 4 y	Network model	Cypher® vs BMS: 0.88[b] (0.55, 1.30) diabetes Taxus® vs BMS 0.91[b] (0.60, 1.30) diabetes Cypher® vs BMS: 1.02 (0.77, 1.29) no diabetes Taxus® vs BMS 0.90 (0.67, 1.16) no diabetes
Kumbhani et al.[42] (2008)	2951	No	6–12 mo	Diabetes only	Cypher® vs BMS 0.64 (0.32, 1.28; p = 0.20)
Gurm et al.[43] (2008)	7455	No	6–12 mo		Cypher® vs Taxus®: 0.88 (0.61, 1.25; p = 0.46)
Schömig et al.[44] (2007)	8695	Yes	9–37 mo	Inter-DES	Cypher® vs Taxus®: 0.92 (0.74, 1.13; p = 0.43)
Kastrati et al.[45] (2007)	2476	Yes	12–24 mo	AMI	DES vs BMS: 0.76 (0.53, 1.10; p = 0.14)
Pasceri et al.[47] (2007)	1857	No	12 mo	AMI	DES vs BMS: 0.90 (0.53, 1.51)
Stone et al.[48] (2007)	5321	Yes	2–4 y		Cypher® vs BMS: 1.27 (0.86, 1.88; p = 0.23) Taxus® vs BMS: 0.94 (0.70, 1.26; p = 0.68)
Kastrati et al.[49] (2007)	4958	Yes	12–59 mo		Cypher® vs BMS: 1.03 (0.80, 1.30)
Spaulding et al.[81] (2007)	1748	Yes	4 y		Cypher® vs BMS: 1.24 (0.84, 1.83; p = 0.28)
Stettler et al.[50] (2007)	18023	No	Up to 4 y	Network model	Cypher® vs BMS: 1.00 (0.82, 1.25) Taxus® vs BMS: 1.03 (0.84, 1.22) Cypher® vs Taxus®: 0.96 (0.83, 1.24)
Nordmann et al.[13] (2006)	8221 1446	No	1 y 4 y		DES vs BMS: 0.94 (0.66, 1.34) DES vs BMS: 1.46 (0.92, 1.31)
Schampaert et al.[51] (2006)	1510	Yes	2 y		Cypher® vs BMS: 1.32 (0.62, 2.78; p = 0.57)
Roiron et al.[53] (2006)	8987	No	12 mo		DES vs BMS: 1.02 (0.64, 1.64; p = 0.92)
Kastrati et al.[54] (2005)	3669	No	6–13 mo	Inter-DES	Cypher® vs Taxus®: 0.86 (0.49, 1.50; p = 0.56)
Indolfi et al.[82] (2005)	3438	No	6–12 mo		DES vs BMS: 1.11 (0.58, 1.10)

a Meta-analyses of DES vs BMS or Cypher® vs Taxus®, reporting mortality as a primary safety endpoint.

b Analysis restricted only to trials prescribing >6 months of dual anti-platelet therapy.

AMI = acute myocardial infarction; **BMS** = bare metal stents; **DES** = drug-eluting stents; **OR** = odds ratio; **RR** = relative risk.

found no increase in definite or probable stent thrombosis out to 4 years (1.5% with Cypher® vs 1.7% BMS [absolute difference –0.2; 95% CI –1.5, 1.0; p = 0.70] and 1.8% vs 1.4% Taxus® vs BMS [absolute difference 0.4; 95% CI –0.7, 1.4; p = 0.52]).

Data from Stone et al.[48] on 5261 patients also reported no significant differences in rates of stent thrombosis between Cypher® versus BMS (1.2% vs 0.6%; p = 0.20) and Taxus® versus BMS (1.3% vs 0.9%; p = 0.30) at 4 years. However a slight excess of late thrombotic events (>1 year) was noted with both Cypher® and Taxus® compared with BMS (five cases vs none [p = 0.025] and nine cases vs two cases [p = 0.025], respectively). The meta-analysis by Stettler et al.[50] revealed overall similar mortality between DES and BMS (HR 1.00 [95% CI 0.82, 1.25] for Cypher® vs BMS; 1.03 [95% CI 0.84, 1.22] for Taxus® vs BMS; and 0.96 [95% CI 0.83, 1.24] for Cypher® vs Taxus®). There were no significant differences in the risk of definite stent thrombosis out to 4 years. However, the risk of late definite stent thrombosis (>30 days) was increased with Taxus® (HR 2.11 [95% CI 1.19, 4.23; p = 0.017] vs BMS; 1.85 [95% CI 1.02, 3.85; p = 0.041] vs Cypher®). Similarly our meta-analysis of Cypher® versus Taxus® suggested a lower rate of stent thrombosis out to 30 months with Cypher® (HR 0.66; 95% CI 0.46, 0.94; p = 0.02).[44]

It has been suggested that the Endeavor® stent might be expected to have a safety edge in terms

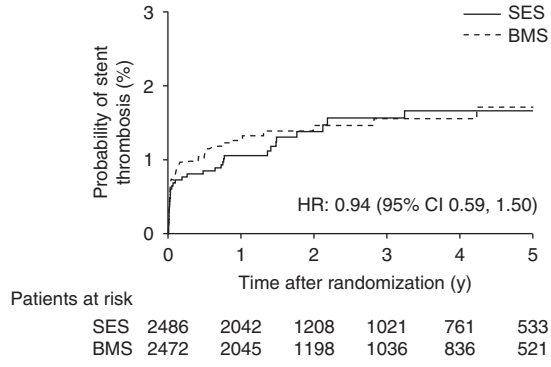
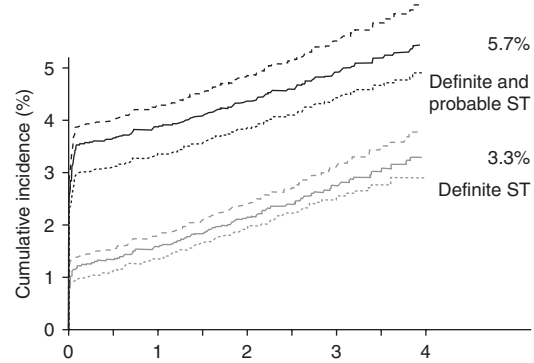


Fig. 4. Stent thrombosis outcomes (without censoring) from a meta-analysis comparing sirolimus-eluting stents (SES) with bare metal stents (BMS).[42] **HR** = hazard ratio.

of a lower rate of stent thrombosis in comparison with other DES,[86] although the deduction that higher degrees of late loss might translate into lower risk of stent thrombosis remains questionable. In fact, data from the SORT OUT III trial raised concern about a higher rate of stent thrombosis with Endeavor® (HR 4.61; 95% CI 1.33, 16.1) at 9 months, although admittedly this timepoint is unsuitable for the assessment of long term safety.[29]

5.3 Registry Reports

Registry data may be particularly important in examining infrequently occurring safety events. A Bern-Rotterdam collaboration observed a steady occurrence of late stent thrombosis out to 4 years, at a rate of approximately 0.4–0.6% per annum (figure 5).[87] Of interest, no effect of the differing duration of DAT prescribed at each of the two centres (3–6 months vs 12 months) was observed. This is of relevance to the associated issue of whether a possible increased risk of stent thrombosis may be attenuated by prolonging the duration of DAT post-intervention. Acute coronary syndrome, age and use of paclitaxel-eluting stents were predictors of late thrombotic events. A number of recent observational comparative studies have provided some reassurance on DES safety. The DEScover registry reported that, after adjustment, a trend for lower rates of death or MI was observed with DES (HR 0.74; 95% CI 0.52, 1.07).[88] Abbott et al.[89] found no difference in mortality between DES and BMS (HR 0.97; 95% CI 0.66, 1.43) in a US National Heart Lung and Blood registry. Jensen et al.[90] report a DES versus BMS HR for death of 0.90 (95% CI 0.75, 1.29) and for stent thrombosis of 0.91 (95% CI 0.67, 1.24). However, these studies were limited to 12- to 15-month follow-up. The REAL registry extended surveillance to 2 years, reporting a non-significant mortality reduction with DES (6.8% vs 7.4%; $p = 0.35$), but a trend towards higher rates of stent thrombosis (1.0% vs 0.6%; $p = 0.09$).[91] The Ontario, Canada, DES registry included 3751 pairs of patients with follow-up out to 3 years and found lower mortality in DES patients compared with propensity-matched BMS patients (7.8% vs 5.5%; $p < 0.001$).[92] A Cleveland Clinic registry (OH, USA) analysis ($n = 8032$) reported that despite extensive adjustment for multiple confounders, DES was associated with significant mortality reduction compared with BMS (0.54; 95% CI 0.45, 0.66; $p < 0.001$).[93] Similarly, Kirtane et al.[56] recently published a large-scale analysis including pooled data on



Months	1	12	24	36	48
Cumulative incidence definite ST (%)	1.2	1.6	2.1	2.7	3.3
Cumulative incidence probable and definite ST (%)	3.7	4.1	4.6	5.2	5.7
Patients at risk	7537	7209	5157	2747	1051

Fig. 5. Stent thrombosis outcomes from two-centre registry data of drug-eluting stents (reproduced from Wenaweser et al.,[87] with permission from Elsevier). **PCI** = percutaneous coronary intervention; **ST** = stent thrombosis.

182 981 registry patients and found a significant reduction in death with DES versus BMS (HR 0.80; $p < 0.001$). It must be acknowledged that residual confounding remains a likely explanation for many of these results.

Meta-analyses of randomized clinical trials do not include off-label use (table II), which, as we have seen, accounts for more than 50% of DES implantation and may be expected to exacerbate any DES-related safety effects. In this respect, data from Beohar et al.[24] are reassuring, showing no difference in the primary endpoint of death, MI or stent thrombosis between off-label and on-label DES use (adjusted HR 1.10; 95% CI 0.79, 1.54; $p = 0.57$). These findings agree with those of Marroquin et al.[26] In the study of Win et al.,[25] stent thrombosis occurred more frequently at 1 year with off-label DES use (1.6% vs 0.9%, HR 2.29; 95% CI 1.02, 5.16; $p = 0.05$); however, if the excess of events in the initial 30 days is excluded (these events are likely reflective of procedural complexity rather than DES-specific effects), this excess becomes non-significant.

There are two patient subgroups where particular safety concerns have been raised: patients requiring stenting following acute MI and patients with diabetes.

5.4 DES Implantation Following Acute Myocardial Infarction

Particular concerns have been raised about the biological effects of DES implantation at a site of plaque rupture and thrombotic occlusion, such as that which may be seen with acute MI. Among other effects, it is proposed that stent implantation at the area of a ruptured plaque (with penetration of the necrotic core) may exacerbate delayed healing. In addition, dissolution of the thrombus jailed at index stenting may predispose to late stent malapposition; both of these factors are risks for late stent thrombosis.[94,95] Interestingly, two registry analyses have recently reported markedly divergent findings. The GRACE (Global Registry of Acute Coronary Events) trial investigators reported a significant increase in late mortality (between 6 months and 2 years) in ST elevation MI (STEMI) patients treated with DES as opposed to BMS (HR 4.90, $p = 0.01$).[96] In marked contrast, interrogation of the US Massachusetts state database of 7211 patients who underwent stenting after acute MI found significantly lower 2-year mortality in DES versus BMS-treated patients (10.7% vs 12.8%; $p = 0.02$).[97] As with all observational data, in spite of propensity score adjustment for measured confounders, the possibility for residual confounding remains. For example, in this latter case, differential size of infarct, duration of DAT and completeness of revascularization (all of which were unmeasured) may explain the authors' findings.

In terms of randomized control trials, consistent benefit has been observed with the Cypher® stent when compared with BMS across a number of studies.[98-102] On the other hand, an initial trial of Taxus® in the setting of PCI failed to detect superiority over BMS.[103] Subsequently however, the findings from the stent arm of the large-scale HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial found no differences in the rate of death or MI between Taxus® and BMS, although noted a significant difference in favour of Taxus® in terms of TLR.[104] In addition, investigators from our centre performed a dedicated meta-analysis based on data from eight studies with mean follow-up durations of 12–24 months. The overall risk of stent thrombosis (HR 0.80; 95% CI 0.46, 1.39; $p = 0.43$), death (HR 0.76, 95% CI 0.53, 1.10; $p = 0.14$) and recurrent MI (HR 0.72; 95% CI 0.48, 1.08; $p = 0.11$) were not significantly different for patients receiving DES versus BMS.[45] Recently, an updated meta-analysis from Brar et al.[55] confirmed lack of mortality differences between DES and BMS though follow-up was typically 12 months or less. Although the data from randomized trials and meta-analyses seem reassuring, follow-up beyond 2 years remains a notable gap at this current point in time.

5.5 DES in Patients with Diabetes Mellitus

Although the introduction of DES therapy seems to have negated the increased risk of resten-

osis associated with diabetes, the risk of death and thrombotic events remains higher in diabetic patients.[105,106] In fact, the meta-analysis of Spaulding et al.[81] reported an increased risk of death associated with Cypher® implantation in diabetic patients compared with BMS. Registry data also initially suggested evidence of high rates of stent thrombosis following DES implantation in diabetic patients.[107-109] A subsequent large registry from the Massachusetts Data Analysis Centre certainly showed no sign of an adverse safety signal with DES versus BMS.[110] In fact, the unadjusted cumulative incidence of mortality at 3 years was lower with DES (14.4% vs 22.2%; $p < 0.001$). Based on propensity-score analysis of 1 : 1-matched DES versus BMS patients, the risk-adjusted mortality and MI rates were 17.5% versus 20.7% ($p = 0.02$) and 13.8% versus 16.9% ($p = 0.02$), respectively.

The Bern group have recently constructed a second collaborative network meta-analysis, this time with the specific aim of comprehensively comparing the effectiveness and safety of Cypher®, Taxus® and BMS in patients with and without diabetes.[41] From a safety standpoint, they found considerable network inconsistency regarding overall mortality in diabetic patients. There was a clear-cut trend towards an increased mortality associated with Cypher® when compared against BMS (RR 1.41; 95% CI 0.95, 2.08), whereas no such trend was observed with Taxus® (RR 0.91; 95% CI 0.58, 1.43); in contrast with these findings, when they examined trials directly comparing Cypher® and Taxus®, a trend was seen in favour of Cypher® (RR 0.86; 95% CI 0.60, 1.24). The authors noted an apparent relationship with duration of DAT and therefore performed a restricted analysis on trials prescribing >6 months of therapy, finding that this removed the observed inconsistency and resulted in HRs near 1 for all safety comparisons between Cypher®, Taxus® and BMS. The conclusion seems to be that diabetic patients may be at particularly high risk of stent thrombosis if they do not receive at least 6 months of DAT after DES.

One further notable consequence of the fall out from the safety concerns relating to DES implantation has been the increasing realization of the importance of universal tools and protocols for the assessment of newer DES technologies. In particular, a role for the EU Commission in preparing a unified guidance document for DES assessment in Europe has been advocated, as well as a call for harmonization of registry protocols and randomized trial designs and standardization of endpoint definitions.[15,80]

As the smoke clears from the great DES safety debate, what conclusions can be drawn? It seems reasonable to conclude that at 4–5 years post-stent implantation (i) there is no increased risk of death or MI with DES and neither is there a general signal of mortality reduction with DES; (ii) there is very little, if any, increased risk of stent thrombosis with DES; and (iii) there may be a difference in the time distribution of thrombotic events after PCI, i.e. a slight excess of stent thrombosis with BMS up to 6 months post PCI and a slight excess of very late stent thrombosis (>1 year post PCI) with DES. This may be related to the duration of DAT.

6. Cost Effectiveness

The issue of cost effectiveness is complex due to constantly changing costs and reimbursements, regional variations and differences in insurance systems. The BASKET (Basel Stent Kosten Effektivitäts Trial) randomized 826 patients to DES or BMS. In terms of death, MI or TLR, the DES outperformed the BMS (7.2% vs 12.1%; OR 0.56; 95% CI 0.35, 0.91; $p = 0.02$).[111] However, in terms of the primary endpoint of cost effectiveness at 6 months, a DES strategy was associated with significantly higher costs compared with BMS (€10 544 ± 6849 vs €9639 ± 9069; $p < 0.001$). Subgroup analysis suggested that DES might be cost effective in higher risk patients, such as those treated with three-vessel disease, those aged >65 years, those with smaller stented vessels (≤2.5 mm) or those with a stent length >20 mm. Analysis of the SIRIUS study by Cohen et al.[112] reported that while DES therapy did not appear to be *cost saving* compared with BMS, the use of Cypher® appeared to be *cost effective* (in terms of quality-adjusted life-years gained), at least in a US healthcare context.

A systematic review of the cost effectiveness of DES was performed by the Liverpool Reviews and Implementation Group. They found a RR of TLR with DES of 0.24 (95% CI 0.19, 0.31) compared with bare metal stenting. However, despite this very significant reduction in TLR, they considered that the balance of evidence supported DES use only in high-risk patients and that DES could be considered cost effective in only a small proportion of these. This study formed an important component of the controversial UK National Institute of Clinical Excellence (NICE) 2007 draft guidelines, which concluded that DES were not cost effective and could not be recommended in patients with coronary disease. This recommendation was subsequently revised in the final 2008 document and concluded that DES remained cost effective in small vessels (<3 mm) and long lesions (>15 mm), provided that the additional costs of the DES are not more than £300.[113] In view of the well established anti-restenotic superiority of DES over BMS, the relevance of such a price differential is perhaps the central consideration in any cost-effectiveness analysis. A price premium of €450 (~£300) for DES, above which cost effectiveness was likely to be lost, was also proposed by the ESC Forum on DES.[80] Finally, in terms of inter-DES differences, our group found evidence that Cypher® implantation may be more cost effective than Taxus® implantation in high-risk patient subsets – a difference driven by costs incurred in re-hospitalization for repeat revascularization.[114]

7. Benefit-Risk Assessment

In terms of the overall impact of thrombosis and restenosis on patient outcomes following DES and BMS implantation, Stone et al.[115] analysed outcomes of patients (with single *de novo* coronary lesions and stable presentations) pooled from the data of four randomized trials of Taxus® versus BMS. With a median follow-up of 3.2 years, TLR (ischemia-driven) was performed in 135 patients in the Taxus® group versus 290 BMS patients (absolute difference 155 events). On the other hand, stent thrombosis occurred in 20 patients in the Taxus® group and 14 BMS patients (absolute difference six events; net absolute difference in events 149, in favour of DES). However, restenosis was associated with death or MI in 3.5% of cases, whereas stent thrombosis had this consequence in 91.1%. Consequently, overall the balance sheet of death or MI read 23 patients in the Taxus® group (4 following TLR, 19 following stent thrombosis) and 23 patients in the BMS group (11 following TLR, 12 following stent thrombosis). It should be noted that the rate of MI after restenosis/TLR presentation is much lower than the ~10% rate published elsewhere,[116] and may conceivably have underestimated the DES benefit. However, the overall finding of no differences in terms of death or MI is in keeping with the findings of many meta-analyses already considered.

Along related lines, Garg et al.[117] sought to quantify at what level of increased risk of stent thrombosis with DES, a universal treatment strategy based on DES would remain superior to BMS implantation. Based on a quality-adjusted life expectancy (QALE) model, they estimated that in the setting of no increased risk of stent thrombosis beyond 1 year, DES would be the preferred choice. On the other hand, at a magnitude of increased risk of stent thrombosis of 0.13% per annum, QALE would be equivalent with both approaches. The authors concluded that a small increase (>0.14%/year) in stent thrombosis with DES would make BMS the preferred approach for the overall PCI population.

The benefit-risk balance of DES and BMS is confounded by one further issue; namely, the ability to comply with DAT for 6–12 months post-intervention. Recent guideline revisions have recommended a duration of DAT after DES implantation of at least 12 months (bleeding risks permitting).[118] Such recommendations are limited by a weak evidence base.[119] Certainly premature discontinuation of DAT following DES implantation is a strong predictive factor for stent thrombosis.[75] Six months of DAT after DES implantation seems to be the minimum duration that can be recommended; patients deemed unlikely to comply with 6-month DAT (either due to patient reliability or, in some jurisdictions, patient cost considerations) or

those requiring urgent non-cardiac surgery within this timeframe should be treated with a BMS (although an argument could be made that plain balloon angioplasty is a reasonable alternative). The real issue is whether or not to recommend universal prolongation of DAT beyond this 6-month timeframe. Two studies with contradictory findings should be mentioned. Airoldi et al.[120] looked at the thrombosis rate with and without clopidogrel, and found that within the first 30 days the risk of stent thrombosis was significantly greater for patients who stopped clopidogrel (4.2%) than for patients who continued to receive it (0.9%). While this excess risk continued out to 180 days, discontinuation of clopidogrel therapy after 6 months did not predict occurrence of stent thrombosis. This may be an indication that 6 months of therapy is sufficient. On the other hand, an interesting observational study from the Duke Heart Center, based on a landmark analysis of event-free patients, appeared to show that ongoing clopidogrel use beyond 6 and even 12 months continued to predict lower rates of death and MI.[121] In actual fact, there appears to be clinical equipoise on this issue, and it is hoped that this will be addressed in the ongoing ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting) study (clinicaltrials.gov identifier NCT00661206).[122]

8. Conclusions

In our interpretation of the available data, it seems reasonable to deduce that the benefit of DES therapy in reducing restenosis is of the order of 35–70% and seen across a broad spectrum of patients and lesions encompassing both on-label and off-label indications. This may translate into an absolute risk reduction of 5–20%, or a number needed to treat of 5–20 patients to prevent one episode of TLR.

The evidence does not support an increased risk of stent thrombosis with DES therapy, at least out to 4–5 years, although there may be a discrepancy in the time course of events with a slight excess of stent thrombosis observed with BMS in the first 6 months and with DES beyond 1 year. However, sufficiently powered dedicated trials to assess this endpoint are lacking. Specific concerns regarding DES implantation in patients presenting with acute MI or in patients with diabetes have not been borne out although additional data on these subgroups (including longer duration of follow-up) are awaited.

Overall, the net clinical benefit is in favour of DES therapy and appears to be consistent across different patient groups. BMS implantation is indicated in cases of urgent requirement for non-cardiac surgery after intervention and in situations where a patient is deemed unlikely to comply with DAT for 6 months. Cost effectiveness of DES therapy is likely to be observed where the cost differential between DES and BMS is less than €450.

There can be few areas in modern medicine that have generated as much data or debate as the field of coronary DES implantation. Evidence for their efficacy in reducing clinical restenosis is consistent. Concerns regarding a higher risk of thrombotic occlusion and patient mortality in the short to medium term following DES implantation have not been borne out after unprecedented systematic data analysis. On the balance of benefit and risk data available, DES implantation should be the preferred approach across the spectrum of patients with obstructive coronary disease who require PCI therapy.

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