Are Drug-Eluting Stents Safe and Effective in the Long Term?

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Abstract
The introduction of drug-eluting stents in 2002 revolutionized interventional cardiology by minimizing restenosis. Reports of increased late stent thrombosis with these stents compared with bare metal stents, probably due to delayed endothelialization, emerged late in 2006. These studies contained serious methodological flaws, however. Subsequent meta-analyses clearly showed only a small incremental risk of late stent thrombosis across all patient groups. Importantly, a significant and sustained benefit of drug-eluting stents due to reduced restenosis and thus repeat revascularization was also shown. Several ‘real-world’ registries have confirmed these results and suggested that the use of these stents in more complex situations is not associated with adverse outcomes. Stent thrombosis is a multifactorial problem, in which the stent is only one element. Further research is required to determine optimal procedural technique and antiplatelet regimens. Drug-eluting stents are safe and effective in the long-term, though intensive research continues into ways to reduce the risk of stent thrombosis in the next generation.

Introduction
Drug-eluting stents (DES) arrived in the world of percutaneous coronary intervention (PCI) in 2002, and almost immediately began to change modern cardiology. The use of standard bare-metal stents (BMS) had vastly reduced the incidence of emergency coronary bypass grafting (CABG) and acute vessel thrombosis during the 1990’s (Figure 1).1,2

DES were shown in randomized trials to deal with the remaining drawback of stents, the occurrence of restenosis. The six-month follow-up of the RAVEL study confirmed a 0% rate of restenosis, target vessel revascularization (TVR) and stent thrombosis.3 The SIRIUS study showed that sirolimus-eluting stents (SES) were associated with a highly significant reduction in in-segment restenosis compared with BMS, and that this difference was evident across the range of patient and lesion characteristics.4 The TAXUS IV study showed similar results with paclitaxel-eluting stents (PES).5

The end of DES?
The first clouds appeared on the horizon in early 2004, however, with a report detailing 4 patients who had suffered stent thrombosis more than 11 months after DES implantation following discontinuation of antiplatelet therapy.6 Doubts were also raised following a histological study of DES months after implantation, in which delayed endothelialization was evident.7 The authors linked this delay with a higher risk of stent thrombosis in DES in comparison with BMS. Subsequently the BASKET-LATE registry study, which followed patients up to 18 months post-stenting, showed an increased frequency of late stent thrombosis and cardiac death or myocardial infarction (MI) following cessation of clopidogrel in patients treated with DES in comparison with BMS (Figure 2).8

The real backlash against DES started at the European Society Congress in September 2006, when Camenzind presented a meta-analysis of randomized trials on first-generation DES showing a higher frequency of death and Q-wave MI in patients treated with DES in comparison with BMS.9 The results were not statistically significant but did show a clear trend between 18 months and 3 years after stent implantation, both for PES and SES. In another high profile presentation, Nordmann suggested that SES were associated with a significant increase in non-cardiac mortality at 2 and 3 years of follow-up when compared with BMS.10 These reports led to sensational headlines in the mass media including newspapers like The New York Times and The Wall Street Journal. However, there were two major methodological limitations to the Camenzind et al.10 and Nordmann et al.10 studies. Firstly, neither was a true meta-analysis, since the data used were collated from papers and presentations rather than ‘patient-level’ information. Secondly the definitions of stent thrombosis varied between the included studies to such an extent that coherent meta-analysis was invalid. Despite this, DES penetration in the US fell by 12% in the six months following the ESC, while in Europe the steady rise in use was halted, and penetration remained fixed at 50%.11,12

There were two immediate positive outcomes from the inappropriate hysteria about DES thrombosis. The first was the development of accepted definitions of stent thrombosis by the Academic Research Consortium (ARC) at the behest of the FDA prior to a special meeting of their advisory panel on...
Figure 1 - Restenosis, the Achilles heel of angioplasty, and the effect of DES.

Figure 2 - Late stent thrombosis and related clinical events in the BASKET-LATE study. DES - green; BMS - blue. Low overall rates with non-significant differences.

DES safety in December 2006. A second positive outcome was that independent meta-analyses were performed on the many studies of DES and BMS using ‘patient-level’ data to provide a clearer answer to this question.

The real risk of stent thrombosis with DES

An edition of the New England Journal of Medicine in February 2007 contained several such studies. A meta-analysis of the incidence of stent thrombosis in 8 major randomized
studies found no significant difference between patients treated with DES and BMS using the ARC definitions (definite or probable stent thrombosis in SES 1.5% vs BMS 1.7%, p=0.70; and PES 1.8% vs BMS 1.4%, p=0.52) (Figure 3)\(^14\). Another meta-analysis of 9 randomized trials concluded that stent thrombosis after one year was more common with PES and SES than BMS, although both DES were associated with a marked reduction in target-lesion revascularization (TLR).\(^{15}\) At 4 years there were no significant differences in the cumulative event rates of death or MI (Figure 4). Similarly a meta-analysis of 4 trials comparing SES and BMS showed no significant differences between the two treatments in terms of death, MI or stent thrombosis up to four years post-stent insertion\(^{16}\).

In the same edition, however, the Swedish Coronary Angiography and Angioplasty registry (SCAAR) found an increased rate of death in patients treated with DES in comparison with BMS at 3 years (adjusted relative risk (RR) 1.18, 95% confidence interval (CI) 1.05 to 1.37)\(^{17}\). Interestingly after an additional year of follow-up, providing a total of 13,786 DES and 21,480 BMS patients, there was no significant difference in mortality between the two groups (RR 1.03, 95% CI 0.94 to 1.14)\(^{18}\). Other large scale ‘real-world’ registries have similarly reported comparable or lower mortality between the two groups\(^{19-22}\). These ‘real world’ registries have also suggested that use of DES in more complex situations is not associated with adverse outcomes.

Perhaps the most important study following the DES ‘crisis’ has been the network meta-analysis that included all relevant studies of first-generation DES\(^23\). The authors included 38 trials with a total of 18,023 patients and a follow-up of up to 4 years. Mortality was similar between SES, PES and BMS (Figure 5). There were no significant differences in the risk of definite stent thrombosis (0 days to 4 years). On the basis of a more marked reduction in TLR in SES than PES-treated patients, and a lower frequency of MI in the SES-treated patients, the authors concluded that SES appeared clinically better.

The concerns raised in previous studies about the risk of stent thrombosis in diabetic patients were also addressed in a recent meta-analysis of diabetic and non-diabetic patients in 5 randomized trials comparing PES and BMS\(^24\). At 4-year follow-up the authors found no significant differences between PES and BMS regarding death (8.4% vs 10.3%, p=0.61), MI (6.9% vs 8.9%, p=0.17) or stent thrombosis (1.4% vs 1.2%, p=0.92). They did find a significant reduction in TLR in the PES-treated patients (12.5% vs 24.7%, p<0.0001).

As a result of all these studies, the safety of DES has been proven. A higher risk of late stent thrombosis may be the result of a drug coating that reduces longer-term ischemia due to restenosis. Indeed the risk of stent thrombosis following DES in a small proportion of patients has been shown to be offset by the benefit in reducing TLR in much higher proportion of
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Figure 4 - Kaplan-Meier curves representing the estimated 4-year cumulative incidence rates of stent thrombosis (A), death (B), myocardial infarction (C) and target lesion revascularization (D) for the pooled randomized trials of paclitaxel-eluting stents and bare metal stents. Median duration of follow-up 3.2 years.

The spotlight on stent thrombosis, its causes and how to reduce it

The greatest benefit of the DES controversy has, however, been the resulting spotlight on stent thrombosis and how to prevent it. The multifactorial nature of stent thrombosis has long been recognized (Figure 6). Indeed late stent thrombosis is not a problem limited to DES. Recognized risk factors for stent thrombosis in DES include renal failure, insulin-dependent diabetes mellitus, calcified lesions, impaired ventricular function, stent underexpansion and residual reference segment stenosis. Recently interest has been growing in the field of responsiveness to antiplatelet treatment with clopidogrel and aspirin. High post-treatment platelet reactivity is one of the best ways to assess clopidogrel nonresponsiveness and has been shown to be an independent risk factor for stent thrombosis in patients receiving DES on multivariate analysis. Individual responsiveness to clopidogrel may be influenced by genetic and cellular factors as well as clinical factors such as patient compliance or clopidogrel dose (Figure 7). Patients with diabetes mellitus may be particularly susceptible to problems of nonresponsiveness to antiplatelet treatment. In a study of 54 diabetic patients who had been taking long-term dual antiplatelet therapy, withdrawal of clopidogrel was associated with both proinflammatory and prothrombotic effects. In another study comparing aspirin responsiveness at different dosages in diabetics and non-diabetics, patients with diabetes had a higher prevalence of aspirin resistance at a dose of 81 mg per day (27% vs 4%; \( p=0.001 \)). Higher doses of aspirin significantly decreased aspirin resistance in diabetics. In a study of 135 patients with coronary artery disease on long-term dual antiplatelet therapy, aspirin resistance was found in 44% of patients, and was more frequent in diabetics than non-diabetics (Figure 8). Optimal management of patients with clopidogrel and/or aspirin resistance remains unclear. Indefinite dual antiplatelet therapy is clearly unfeasible. Testing for resistance to aspirin before cessation of clopidogrel may provide important information, and gradual discontinuation of clopidogrel therapy also warrants further investigation.

Future developments in DES

The spotlight on the deficiencies of first-generation DES has also accelerated the development of the next generation. An antibody-coated stent which aims to enhance vessel healing after PCI is already available and the recommended duration of dual antiplatelet therapy is only one month. Bioabsorbable stents are also of considerable interest in terms of reducing the risk of stent thrombosis. A recent study of 30 patients...
who received a bioabsorbable everolimus-eluting stent showed encouraging results with no late stent thrombosis and a 3.3% major adverse cardiac event rate at 1 year\textsuperscript{19}. Other stents under development that may reduce stent thrombosis include polymerless DES, and a new generation of DES with a biodegradable polymer is coming on the market.

**Conclusions**

First-generation DES are associated with a slightly increased risk of late stent thrombosis when compared with BMS; this is largely due to delayed endothelialization and is not translated into an increased risk of death or MI up to four years of follow-up. This slightly increased risk is compensated
for a large reduction in restenosis and the need for repeat revascularization compared with BMS. Reassuringly also, many large real-world registries have reported low rates of late stent thrombosis even in more complex patient groups.

There have been several beneficial outcomes from the DES backlash of 2006-2007: the development of a uniform definition of stent thrombosis events in research studies, better follow-up in research studies and better collaboration...
and transparency between research institutions and industry. DES have undoubtedly benefited many patients already, and the next generation seems set to extend this to many more.

References


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