Drug-eluting coronary stents — a note of caution

Richard W Harper

ABSTRACT

- There are two types of coronary stents: bare-metal stents (BMS) that cost about $800 each, and drug-eluting stents (DES) that cost about $3300 each.
- DES reduce the rate of restenosis but have a higher incidence of late stent thrombosis, particularly if dual antiplatelet therapy with aspirin and clopidogrel is interrupted.
- Stent thrombosis has a myocardial infarction rate of 70% and a mortality rate of 31%–45%.
- Randomised studies of BMS versus DES show no increase in myocardial infarction or death with DES in simple coronary lesions, but in clinical practice, DES are mainly used in complex coronary disease where the rate of stent thrombosis is higher. Registry data suggest an increased rate of death and myocardial infarction of 0.5%–1.0% per annum with DES.
- Clinicians need to be aware of the risks associated with prematurely ceasing dual antiplatelet therapy in patients with DES.

MJA 2007; 186: 253–255

eMJA RAPID ONLINE PUBLICATION 14 FEBRUARY 2007

Percutaneous coronary intervention (angioplasty) using stents is a common procedure in Australia, with over 30 000 cases performed each year.[1] Two basic stent types are used: bare-metal stents (BMS) that cost about $800 each, and drug-eluting stents (DES) that cost about $3300 each. Until recently, two types of drug-eluting stents have been available: sirolimus- or paclitaxel-eluting stents. Both these drugs have a potent antiproliferative action and are embedded in a non-resorbable polymer matrix completely covering the stent struts, thus allowing slow release of the drug in high concentrations to the local surrounding tissue. The net result is the inhibition of the neointimal hyperplastic response to vessel injury, which is the predominant cause of restenosis with the use of BMS.[2-4]

However, there is a potential downside in the use of DES. Unlike the animal models in which they were tested,[5] in the human atherosclerotic coronary artery, the drugs markedly inhibit or delay endothelialisation of the stent struts,[6,7] thus making the stent more susceptible to thrombosis, particularly if dual antiplatelet therapy with aspirin and clopidogrel is interrupted after implantation.[8,9] Stent thrombosis is a serious complication that causes major myocardial infarction in more than 70% of cases and carries a mortality rate of 31%–45%.[9,10] Opinion varies on the relative susceptibility of DES and BMS to thrombosis, but based on their personal experience, many cardiologists worldwide are convinced that the incidence of late stent thrombosis (ie, more than 30 days post-implantation) is higher with DES. Emerging evidence detailed here, although not entirely consistent, now supports this supposition.

What is the emerging evidence?

Pooled analysis of the inital randomised studies comparing DES with BMS showed a substantial (three- to fourfold) reduction in restenosis at 12 months with DES, but no difference in the more important end points of myocardial infarction and death.[11,12] Nor was there any apparent increased risk of stent thrombosis with DES. However, 4-year follow-up data recently released by the stent manufacturers now indicate a higher rate of stent thrombosis with DES compared with BMS (1.3% v 0.8% for the paclitaxel-eluting stent, and 1.2% v 0.6% for the sirolimus-eluting stent).[13] Nevertheless, according to the manufacturers, this excess risk is not associated with an increased risk of myocardial infarction or cardiovascular death — instead, the increased risk of adverse conseqences due to late stent thrombosis is balanced by a corresponding reduction in risk due to a reduced rate of restenosis and a reduced need for further intervention.[13] Restenosis is a far less serious complication than stent thrombosis, but nevertheless carries approximately a 10% risk of causing myocardial infarction.[14]

Importantly, patients in the randomised studies mentioned above have generally had relatively simple coronary lesions, whereas, in the "real world", DES are frequently used for more complex coronary lesions that have not necessarily been evaluated by these trials. In the United States, it is estimated that this "off-label" use accounts for at least 60% of DES usage;[15] a similar figure almost certainly applies in Australia. The likelihood of stent thrombosis is undoubtedly higher in more complex coronary lesions, and therefore any increased tendency towards stent thrombosis with use of DES is likely to be accentuated. For example, in a large, prospective, observational study of 2229 consecutive patients receiving DES for a wide variety of coronary lesions, the incidence of stent thrombosis at 9 months was 1.3%,[9] compared with an incidence of < 0.5% in the initial randomised studies. Recently presented data from a large European registry where off-label use was common indicate a 0.6% per annum increase in late stent thrombosis with use of DES, compared with BMS.[16] Whether this higher incidence of stent thrombosis translates into a higher rate of myocardial infarction or death in comparison to alternative treatments, such as BMS or coronary artery bypass surgery, has not been tested in randomised studies. However, data from a Swedish registry of all patients undergoing coronary stenting between 2003 and 2005 ($n = 39\,432$) suggest an increased rate of death and myocardial infarction of 0.5%–1.0% per annum with DES, compared with BMS.[17]

Perhaps the most disconcerting data regarding DES relate to cessation of dual antiplatelet therapy. For BMS, 1 month of therapy with aspirin and clopidogrel following stent implantation is recommended. For DES, the current recommendation for this dual therapy is a minimum of 3 months with the sirolimus-eluting stent and 6 months with the paclitaxel-eluting stent.[18] Compliance with these guidelines is important. In one study, the incidence of thrombosis with use of DES and premature discontinuation of dual therapy was 29%.[9] Another registry study prospectively looked at patients with myocardial infarction who had been treated with DES.[19] It found that 13.6% of patients stopped clopidogrel therapy less than 30 days after stent implantation. At 12 months, the mortality in those who had prematurely ceased clopidogrel therapy was 7.5%, compared with 0.7% in those who had not ($P < 0.001$). Other data suggest that a longer duration of dual

antiplatelet therapy than suggested in the guidelines may be beneficial, particularly if DES are used for more complex cases, as is now routine. A large observational study from Duke University looked at consecutive patients treated with BMS ($n = 3165$) and DES ($n = 1501$).[20] Patients were divided into groups based on whether or not they were taking clopidogrel at 6 and 12 months. No differences were seen between the groups of patients with BMS, but for those with DES, clopidogrel use at both 6 and 12 months was associated with a significantly lower rate of death and myocardial infarction at 24 months (3.1% v 7.2%, $P = 0.02$; and 0 v 4.5%, $P < 0.001$). Equally compelling data come from the recently published Basel Stent Cost-Effectiveness Trial — Late Thrombotic Events (BASKET-LATE).[21] In this study, 746 patients were randomised to receive BMS, sirolimus-, or paclitaxel-eluting DES on a 1:1:1 basis. All were initially treated with aspirin and clopidogrel for 6 months, after which clopidogrel was withdrawn. Although the 18-month combined rate of death and myocardial infarction was not significantly different between the DES and BMS groups (8.4% v 7.5%), at 7–18 months (after clopidogrel had been discontinued), investigators observed an increase in the composite end point of death and myocardial infarction among the DES patients compared with the BMS patients (adjusted hazard ratio, 2.2; $P = 0.03$).

In the US, concerns about the susceptibility of DES to thrombosis have been the subject of much media attention, consumer fear, and debate.[22] An expert panel of the US Food and Drug Administration recently examined the issue of stent thrombosis with DES. They concluded that:

> DES remain safe and effective when used in patients having clinical and coronary anatomic features similar to those treated in the pivotal trials . . .[23]

In these patients, the recommendations regarding the duration of combined aspirin and clopidogrel treatment were unchanged. The expert panel also warned that:

> With more complex patients . . . off-label use of DES is associated with an increased risk of stent thrombosis, death or MI compared to on-label use . . . [In these patients] the optimal duration of antiplatelet therapy . . . is unknown . . .[15]

What are the clinical implications of this emerging evidence about DES?

Based on this emerging evidence, many cardiologists now recommend that patients with DES continue on aspirin and clopidogrel for at least 12 months after implantation, or perhaps indefinitely. Such a policy creates problems in its own right. The treatment is expensive (clopidogrel costs $1020 a year), exposes patients to a 1%–2% per annum increased risk of major bleeding,[24,25] and presents problems if non-cardiac surgery is subsequently required. Indeed, many vascular and orthopaedic surgeons are reluctant to operate on patients using aspirin therapy, let alone dual antiplatelet therapy. Furthermore, antiplatelet therapy may be inadvertently ceased prior to dental or minor surgical procedures because the attending physician is unaware of the risks associated with its cessation.

In the Australian private health sector, DES (which are fully covered by health insurance) are now almost universally used in preference to BMS. In the public health sector, where cost constraints are rigidly enforced, the use of DES is far less. In Victoria, for example, public hospitals are funded for a 30% usage of DES, which means that approximately 70% of patients will receive BMS. DES are mainly reserved for patients thought to be at high risk of restenosis, such as those with diabetes, or with long lesions or small vessels. At regional cardiac society meetings, cardiologists have often expressed concern about the discrepancy in treatment between private and public patients, but based on these recent data, public patients who receive BMS may be at an advantage. Compared with stent thrombosis, restenosis — even if it results in the need for further revascularisation — is a considerably lesser complication. The almost universal practice of using DES in private patients needs to be reviewed.

Obviously, patients who are likely to require non-cardiac surgery in the near future should not have DES if coronary revascularisation is thought advisable before surgery. In patients who have DES, non-cardiac surgery should be delayed, if possible, for at least 12 months after implantation. Where non-cardiac surgery is required within 12 months of implantation, it should preferably be performed with the patient taking at least one antiplatelet agent and, if possible, both. The increased risk of bleeding needs to be balanced against the risk of the extremely serious complication of stent thrombosis. Furthermore, such surgery should be performed in a hospital with 24-hour facilities for emergency coronary angioplasty, which is the optimal treatment should stent thrombosis occur.

As can be seen, DES implantation imposes significant potential limitations on patients.

What of the future?

The initial enthusiasm that greeted DES is now tempered by the realisation that they are associated with an increased incidence, albeit small, of stent thrombosis and its attendant problems. Coronary stenting is the subject of extensive industry-based research, with much work now directed at developing stents that inhibit neointimal hyperplasia, yet enhance endothelialisation. It is possible that newer DES may have a lower incidence of stent thrombosis, but this remains to be proven. The most recent of the DES on the Australian market is a zotarolimus-eluting stent. Early data on this stent indicate an incidence of stent thrombosis similar to BMS at 2 years,[26] but longer follow-up is needed. Novel stent designs include bioabsorbable stents, and stents coated with monoclonal antibodies designed to capture circulating endothelial progenitor cells.[27] It is hoped that these developments will eventually result in a coronary stent with a negligible incidence of both restenosis and thrombosis. Until then, physicians should be aware of the potential problems associated with DES.

Competing interests

None identified.

Author details

Richard W Harper, MB BS, FRACP, FACC, Emeritus Director of Cardiology
Department of Cardiology, Monash Medical Centre, Melbourne, VIC.
Correspondence: richard.harper@med.monash.edu.au

References

1 Australian Institute of Health and Welfare. Australia's health 2004. Canberra: AIHW, 2004. (AIHW Cat. No. AUS 44.)
2 Sigwart U. Drug-eluting stents are safe and effective: right or wrong? *J Am Coll Cardiol* 2006; 47: 1361-1362.
3 Jenkins NP, Prendergast BD, Thomas M. Drug eluting coronary stents. *BMJ* 2002; 325: 1315-1316.
4 Fattori R, Piva T. Drug-eluting stents in vascular intervention. *Lancet* 2003; 361: 247-249.
5 Suzuki T, Kopia G, Hayashi S, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. *Circulation* 2001; 104: 1188-1193.
6 Kotani J, Awata M, Nanto S, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. *J Am Coll Cardiol* 2006; 47: 2108-2111.
7 Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006; 48: 193-202.
8 McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004; 364: 1519-1521.
9 Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005; 293: 2126-2130.
10 Kuchulakanti PK, Chu WW, Torguson R, et al. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. *Circulation* 2006; 113: 1108-1113.
11 Hill RA, Dundar Y, Bakhai A, et al. Drug-eluting stents: an early systematic review to inform policy. *Eur Heart J* 2004; 25: 902-919.
12 Moreno R, Fernandez C, Hernandez R, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol* 2005; 45: 954-959.
13 Boston Scientific. Resources for healthcare professionals. Data on the drug-eluting stent safety debate. http://www.taxus-stent.com (accessed Feb 2007).
14 Chen MS, John JM, Chew DP, et al. Bare metal stent restenosis is not a benign clinical entity. *Am Heart J* 2006; 151: 1260-1264.
15 US Food and Drug Administration. Update to FDA statement on coronary drug-eluting stents. 4 Jan 2007. http://www.fda.gov/cdrh/news/010407.html (accessed Feb 2007).
16 Wenaweser P. Drug-eluting stent: long term follow-up. Presented at the European Society of Cardiology Scientific Congress; 2006 Sep 2-6; Barcelona, Spain.
17 Lagerqvist B, Wallentin L, Lindbäck J, et al. Long-term outcome of DES vs BMS implanted in Sweden 2003–2004. Presented at an Open Public Hearing of the Circulatory System Devices Panel, US Food and Drug Administration, 7 Dec 2006. http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4253oph1_index.htm (accessed Jan 2007).
18 Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention — summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 2006; 47: 216-235.
19 Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcome of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation* 2006; 113: 2803-2809.
20 Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007; 297: 159-168.
21 Pfisterer M, Brunner-La Rocca HP, Buser PT, et al; BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006; 48: 2584-2591.
22 Shuchman M. Debating the risks of drug-eluting stents. *N Engl J Med* 2007; 356: 325-328.
23 US Food and Drug Administration. FDA statement on coronary drug-eluting stents. 14 Sep 2006. http://www.fda.gov/cdrh/news/091406.html (accessed Feb 2007).
24 Collet JP, Montalescot G, Blanchet B, et al. Impact of prior use or recent withdrawl of oral antiplatelet agents on acute coronary syndromes. *Circulation* 2004; 110: 2361-2367.
25 Diener HC, Bogousslavsky J, Brass LM, et al; MATCH Investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004; 364: 331-337.
26 Fajadet J, Wijns W, Laarman GJ, et al; ENDEAVOR II investigators. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for the treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 2006; 114: 798-806.
27 Serruys PW. Fourth annual American College of Cardiology international lecture: a journey in the interventional field. *J Am Coll Cardiol* 2006; 47: 1754-1768.

(Received 18 Jan 2007, accepted 6 Feb 2007) ❑