

The Canadian Association of Interventional Cardiology and the Canadian Cardiovascular Society joint statement on drug-eluting stents

Michael P Love MB ChB MD¹, Erick Schampaert MD², Eric A Cohen MD³, John G Webb MD⁴, Todd J Anderson MD⁵, Marino Labinaz MD⁶, Jean-François Tanguay MD⁷, Vladimír Džavík MD⁸; for the Canadian Association of Interventional Cardiology and the Canadian Cardiovascular Society

MP Love, E Schampaert, EA Cohen, et al; for the Canadian Association of Interventional Cardiology and the Canadian Cardiovascular Society. The Canadian Association of Interventional Cardiology and the Canadian Cardiovascular Society joint statement on drug-eluting stents. *Can J Cardiol* 2007;23(2):121-123.

Recent reports of late stent thrombosis events following deployment of drug-eluting stents (DES) have raised concerns about their safety and role in the management of coronary artery disease. The Canadian Association of Interventional Cardiology and the Canadian Cardiovascular Society have carefully examined the available evidence, including the data presented at the recent Food and Drug Administration Circulatory System Devices Advisory Panel meeting. The purpose of the present statement is to summarize the available evidence relating to DES thrombosis and to provide practical recommendations regarding DES use and antiplatelet therapy.

Key Words: Angioplasty; Stents; Thrombosis

Before the availability of drug-eluting stents (DES), in-stent restenosis was the major complication limiting the long-term efficacy of percutaneous coronary intervention. Early clinical studies in selected patients with noncomplex coronary lesions raised hopes that restenosis could be eliminated by DES (1). Subsequent trials in more complex lesions confirmed a substantial reduction in restenosis and target lesion revascularization rather than complete abolition of these adverse events (2). DES use rates subsequently escalated rapidly, and quickly reached 90% of total stent use in the United States and some European countries.

Funding restrictions have resulted in lower DES use rates in Canada. Approximately 35,000 DES were implanted across Canada during 2005, representing just over 40% of all stents used (unpublished data). Two DES have been approved by Health Canada: the paclitaxel-eluting Taxus stent (Boston Scientific Corporation, USA) and the sirolimus-eluting Cypher stent (Cordis Corporation, USA). A third DES, the zotarolimus-eluting Endeavor stent (Medtronic Incorporated, USA), is available through Health Canada's Special Access Programme, but has yet to receive full approval.

Document de principes conjoint de l'Association canadienne de cardiologie d'intervention et de la Société canadienne de cardiologie sur les endoprothèses à élution médicamenteuse

Les récents comptes rendus de thromboses tardives sur endoprothèse après l'installation d'endoprothèses à élution médicamenteuse (EÉM) ont soulevé des inquiétudes quant à l'innocuité et au rôle de ces instruments dans la prise en charge des coronaropathies. L'Association canadienne de cardiologie d'intervention et la Société canadienne de cardiologie ont examiné attentivement les données probantes disponibles, y compris les données présentées au récent groupe consultatif sur les instruments de l'appareil circulatoire de la *Food and Drug Administration*. Le présent document de principes vise à résumer les données probantes au sujet de la thrombose sur EÉM et à fournir des recommandations pratiques sur l'utilisation des EÉM et de la thérapie antiplaquettaire.

Multiple studies have confirmed that stent thrombosis occurring at any time point following either bare metal stent (BMS) or DES implantation is a very serious adverse event associated with high rates of death and nonfatal myocardial infarction (3-7). During 2006, dissemination of the results of the Basel Stent Cost-effectiveness Trial – Late Thrombotic Events (BASKET-LATE) (8) and other DES trial meta-analyses (9,10) raised widespread concerns about an increase in late (more than 30 days) and very late (more than 12 months) stent thrombosis in patients treated with DES compared with those receiving BMS. Based on these and a number of other reports, the Food and Drug Administration (FDA) Circulatory System Devices Advisory Panel met in December 2006 (11) and reviewed an exhaustive array of data in an attempt to characterize the risks, timing and frequency of DES thrombosis.

The FDA panel reaffirmed that the use of both Taxus and Cypher DES in accordance with their approved labelling is associated with a significant and persistent long-term reduction in restenosis and clinically driven repeat target lesion revascularization compared with BMS. There is, however, evidence of a small increase in very late stent thrombosis, which

¹Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia; ²Hôpital du Sacré Cœur, Montreal, Quebec; ³Sunnybrook Health Sciences Centre, Toronto, Ontario; ⁴St Paul's Hospital, Vancouver, British Columbia; ⁵Foothills Hospital, Calgary, Alberta; ⁶University of Ottawa Heart Institute, Ottawa, Ontario; ⁷L'institut de cardiologie de Montreal, Montreal, Quebec; ⁸University Health Network, Toronto, Ontario
Correspondence and reprints: Dr Michael Love, Division of Cardiology, Queen Elizabeth II Health Sciences Centre, 5955 Veteran's Memorial Lane, Halifax, Nova Scotia B3H 3A7, e-mail michael.love@cdha.nshealth.ca; Dr Vladimír Džavík, Division of Cardiology, University Health Network 6-246 EN, Toronto General Hospital, Toronto, Ontario M5G 2C4, e-mail vlad.dzavik@uhn.on.ca
Received and accepted for publication January 22, 2007

emerges one to four years after DES implantation; the absolute risk is approximately 0.2% higher per year than after BMS implantation (11-13). Based on the available data, this small increase in very late thrombosis after DES implantation is not associated with an increased overall risk of death or nonfatal myocardial infarction, compared with patients treated with BMS. There are currently insufficient data to establish whether very late stent thrombosis events will continue to accrue beyond four years of follow-up.

Data on DES use outside of their approved indications are more limited and generally derived from DES registries, which lack a BMS control group and entail only relatively short-term follow-up (one year or less). The so called 'off-label' DES use does appear to be associated with an increased risk of stent thrombosis, myocardial infarction and death, compared with on-label use (11,14). It has been estimated that approximately 60% of DES use in the United States is off-label. The frequency of such use in Canada is unknown.

Multiple studies have confirmed that premature discontinuation of dual antiplatelet therapy with acetylsalicylic acid and clopidogrel before the end of the minimum recommended treatment period (three months after Cypher stent implantation and six months after Taxus stent implantation) is associated with a substantially increased risk of stent thrombosis (5,15,16). The pathophysiology of late and very late DES thrombosis that occurs after dual antiplatelet therapy is intentionally discontinued is poorly understood. Postulated mechanisms include delayed or incomplete re-endothelialization of the stented segment and an idiosyncratic localized hypersensitivity reaction to the polymer that regulates drug elution (17). The FDA panel concluded that the optimal duration of dual antiplatelet therapy is currently unknown, and whether an extended course will prevent late and very late thrombosis is unclear (14). They recommended that patients treated with DES should receive acetylsalicylic acid indefinitely, in addition to a minimum of three months (for Cypher patients) or six months (for Taxus patients) of clopidogrel; dual antiplatelet therapy should be extended to 12 months in patients at low risk of bleeding. Recently, a number of other professional societies even more strongly endorsed continuing dual antiplatelet therapy for 12 months following DES implantation and for longer than 12 months in patients especially thought to be at increased risk of stent thrombosis (18-20).

CANADIAN ASSOCIATION OF INTERVENTIONAL CARDIOLOGY AND CANADIAN CARDIOVASCULAR SOCIETY POSITION AND RECOMMENDATIONS

After reviewing the available data, the Canadian Association of Interventional Cardiology and the Canadian Cardiovascular Society are in agreement with the findings and recommendations of the FDA Circulatory System Devices Advisory Panel. Very late thrombosis occurring beyond 12 months occurs more frequently after on-label DES implantation than after BMS use. However, the risk is small, and its impact is likely counterbalanced by the reduction in restenosis and repeat target lesion revascularization, such that there is no overall increase in death or nonfatal myocardial infarction.

The following recommendations apply to currently approved DES only. Additional or modified recommendations

may be required as additional data regarding DES safety and antiplatelet therapy become available.

Recommendations for DES use

1. Physicians should always carefully consider the benefits and risks on an individual patient basis when choosing between DES and BMS.
2. Physicians should weigh the benefits and risks especially carefully when considering DES use for unapproved (off-label) indications. While many of these patients may benefit from the significant reduction in restenosis and the need for repeat revascularization through DES implantation, it may be at the expense of a higher risk of very late stent thrombosis.
3. Interventional cardiologists should aim to be meticulous in their stent deployment techniques. High-pressure balloon inflation should be considered to optimize DES deployment, and intravascular ultrasound should be considered when the adequacy of deployment is uncertain.
4. DES should not be deployed in patients who are unable to comply with or tolerate prolonged dual antiplatelet therapy. Reasons may include bleeding risk, side effects, cost issues or a history of noncompliance with other medical interventions. In some situations, the obstacle(s) to prolonged therapy may be overcome with additional education and financial support. However, it is the responsibility of the referring physician, the interventional cardiologist and other members of the health care team to assess this issue carefully via direct questioning and to communicate any concerns actively before a decision is taken to implant a DES.
5. DES should not be deployed in patients who have known upcoming surgical procedures for which dual antiplatelet therapy will need to be discontinued.

Recommendations for antiplatelet therapy

1. It is recommended that all patients treated with DES should remain on dual antiplatelet therapy with acetylsalicylic acid 81 mg to 325 mg daily and clopidogrel 75 mg daily for at least 12 months.
2. Even longer-term dual antiplatelet therapy should be considered in patients treated with DES who are thought to be at higher risk for very late stent thrombosis or in whom stent thrombosis is likely to have fatal consequences (eg, multiple stents, bifurcation stenting or left main stem intervention). Many patients will likely require long-term dual antiplatelet therapy; however, the exact duration of treatment should be determined on an individual patient basis after careful consideration of the competing risks of stent thrombosis and bleeding.

3. Physicians must counsel their patients in clear terms against premature discontinuation of dual antiplatelet therapy. If temporary or permanent premature discontinuation becomes necessary, it must be done in consultation with an interventional cardiologist. If discontinuation of both antiplatelet agents is required in a patient who is thought to be at high risk of stent thrombosis or in whom stent thrombosis would be catastrophic, consideration should be given to temporary anticoagulation with heparin.
4. There is no evidence to support restarting clopidogrel in patients who have completed their course of dual antiplatelet therapy and remained event-free on acetylsalicylic acid monotherapy.

REFERENCES

1. Morice MC, Serruys PW, Sousa JE, et al; RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773-80.
2. Roiron C, Sanchez P, Bouzamondo A, Lechat P, Montalescot G. Drug eluting stents: An updated meta-analysis of randomised controlled trials. *Heart* 2006;92:641-9.
3. Heller LI, Shemwell KC, Huq K. Late stent thrombosis in the absence of prior intracoronary brachytherapy. *Catheter Cardiovasc Interv* 2001;53:23-8.
4. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: A pooled analysis of multicenter coronary stent clinical trials. *Circulation* 2001;103:1967-71.
5. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293:2126-30.
6. 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;113:1108-13.
7. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol* 2005;45:2088-92.
8. Pfisterer ME, 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. *J Am Coll Cardiol* 2006;48:2584-91.
9. Camenzind E, Steg PG, Wijns W. A meta-analysis of first generation drug eluting stent programs. [Hotline Session 1]. The World Congress of Cardiology 2006. Barcelona, September 2 to 5, 2006. (Abst)
10. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: A meta-analysis. *Eur Heart J* 2006;27:2784-814.
11. Food and Drug Administration Clinical Overview for DES Thrombosis Panel. <www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4253b1-index.htm> (Version current at January 24, 2007).
12. Stone GW. Independent physician led patient level analysis: Cypher randomized trials. Transcatheter Cardiovascular Therapeutics 18th Annual Scientific Symposium. Washington, October 22 to 27, 2006. (Abst)
13. Leon MB. Independent physician led patient level analysis: Taxus randomized trials. Presented at Transcatheter Cardiovascular Therapeutics 18th Annual Scientific Symposium. Washington, October 22 to 27, 2006. (Abst)
14. Update to FDA statement on coronary drug-eluting stents. <www.fda.gov/cdrh/news/010407.html> (Version current at January 22, 2007).
15. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: Results from the PREMIER registry. *Circulation* 2006;113:2803-09.
16. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007;297:159-68.
17. 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.
18. British Cardiovascular Interventional Society (BCIS) Council Statement on stent thrombosis and drug eluting stents. <www.bcis.org.uk>
19. Hodgson JM, Stone GW, Michael Lincoff A, et al. Late stent thrombosis: Considerations and practical advice for the use of drug-eluting stents: A report from the society for cardiovascular angiography and interventions drug-eluting stent task force. *Catheter Cardiovasc Interv* 2007 (in press). Available online at <www.scai.org>
20. Grines CL, Bonow RO, Casey DE Jr, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. A science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation* 2007 (in press). Available online at <www.circulationaha.org>