Editorial

Do Drug-Eluting Stents Cause Late Stent Thrombosis?

WAI-HONG CHEN, SHU-KIN LI, CHU-PAK LAU

From Division of Cardiology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR

Since the introduction of balloon angioplasty, restenosis has become the "Achillis tendon" of this mode of percutaneous coronary intervention (PCI). Stent implantation improves but does not eliminate restenosis. However, an iatrogenic disease, namely instent restenosis (ISR), emerges following placement of first-generation bare metal stents (BMS) and may be even more difficult to treat than the parent disease. Over the last few years, multiple randomised clinical trials have demonstrated the efficacy of drug-eluting stents (DES) to substantially reduce angiographic ISR and the clinical need for repeat revascularisation when compared with BMS.[1-4] Moreover, these studies showed no short-term safety concerns, particularly the issue of stent thrombosis. The encouraging initial data led to subsequent widespread adoption of DES in interventional cardiology with utilisation of DES from 50% to >90% of all stent implantation. A recent meta-analysis[5] of randomised controlled trials comparing sirolimus and derivatives or paclitaxel and derivatives eluting stents versus BMS with up to 12 months' follow up demonstrated a significant reduction of major adverse cardiac events (MACE; a composite of death, myocardial infarction [MI], and revascularisation) from 19.9% to 10.1% (odds ratio [OR] 0.46; 95% confidence intervals [CI] 0.41 to 0.52, p<0.001). The benefit is driven by reduction in revascularisation while rates of death and MI were not different between the two groups. Importantly, the occurrence of stent thrombosis was 0.7% with DES versus 0.8% with BMS (OR 0.71; 95% CI 0.41 to 1.25, p=0.24) at 1 year.

In the recent World Congress of Cardiology September 2006, data were presented concerning safety issues of DES which sparked debate in the cardiology community and "hysteria" in lay press and general public. Camenzind showed in a meta-analysis of all Cordis/J & J-sponsored sirolimus-eluting stent (SES) trials and Boston Scientific-sponsored paclitaxel-eluting stent (PES) program that death and Q-wave MI rate was 6.3% in the SES and 3.9% in the BMS group (p=0.03), compared with 2.6% in the PES group and 2.3% in the BMS group (p=NS).[6] Nordmann combined data from 17 randomised trials of SES and PES to evaluate total, cardiac, and non-cardiac mortality. A trend of increased mortality was observed in the DES group with follow up more than 1 year. No significant differences in cardiac mortality were evident between the groups. SES was found to be associated with increased non-cardiac mortality which included cancer, stroke, and lung disease, but this observation was based on low event rates from a few friends.[6] In another presentation, Wenaweser analysed stent thrombosis rates among patients enrolled in the SIRTAX, post-SIRTAX registries, RESEARCH, and T-SEARCH registries. Angiographically documented stent thrombosis occurred in 152 cases out of 8146 patients. The cumulative incidence of stent thrombosis was 2.9%, giving a rate of 1.3 per 100 patient-years.[6] These figures raise concern on the long-term safety of DES use both in randomised trials and in the "real world" setting. However, none of these presentations were published in peer reviewed journals at the time of writing.

Address for reprints: Prof. Chu-Pak Lau
William M.W. Mong Professor in Cardiology, Room 1927, Block K, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong SAR

Tel: (852) 2855 4244; Fax: (852) 2818 6304

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The most recent publication about outcomes of DES use in contemporary PCI came last month. This DEScover registry[7] collected data on 6906 patients undergoing PCI at 140 US centres from January to June 2005. DES (both SES and PES) were used to treat 94% of the lesions while BMS were used in the remaining. At 1 year, the adjusted risk of death or MI was similar between DES-treated and BMS-treated patients (hazard ration 0.74; 95% CI 0.52 to 1.07). Target vessel revascularisation was significantly reduced from 9.5% in the BMS group to 6.0% in the DES group (p=0.007). Rates of stent thrombosis were similar among BMS (0.8%), SES (0.5%), and PES (0.8%) patients.

What should we do amidst the available "confusing" information on the long-term safety of DES? First, peer-reviewed publications by Roiron et al on DES use in the setting of randomised controlled trials and the DEScover registry concerning DES use in the "real world" both showed no increase in stent thrombosis rate at 1 year comparing DES with BMS. Second, it is essential to see published papers to have more complete information, such as the percentage follow up, adherence to antiplatelet therapy, and the definition of stent thrombosis, before reaching a conclusion. The definition of late stent thrombosis is a subject of controversy, with definition ranging from angiographic proven thrombosis to include all unexplained death. Third, we have to balance the possible increased risk of stent thrombosis and the proven benefit of restenosis reduction, remembering that ISR can present with MI and its treatment may have significant procedural complications. It is most important to compare the overall rate of death or MI between different treatment modalities. It is also imperative to adhere to known measures for preventing stent thrombosis. We learn from the CREDO trial[8] that among patients undergoing non-urgent PCI in the BMS era, 1-year of dual antiplatelet therapy using aspirin and clopidogrel was associated with 26.9% relative reduction in death, MI or stroke when compared with a 4-week dual antiplatelet therapy followed by aspirin monotherapy. After DES implantation with the associated delayed endothelialisation, we have evidence to support a more prolonged dual antiplatelet therapy, not only to prevent stent thrombosis but also to reduce adverse ischemic events. Finally, with the high cost and potential long term risk of DES, it is both good medicine and cost effective to use DES in patient or lesion subsets that are associated with the highest risks of restenosis, in which the benefit of DES will be maximum.[9] These include diabetic patients, small reference lumen diameter, long lesions, and at some vessel types and sites (Table).[10]

At present, whether DES is associated with a higher late stent thrombosis rate remains an open

Table. Clinical restenosis rate (%) based on the presence of diabetes and lesion characteristics (Based on reference 10)

	Lenion Length, mm						
Reference Vessel Diameter (mm)	10	15	20	25	30	35	40
Diabetic patients							
2.5	18	21	24	28	33	38	45
3.0	12	14	16	18	21	25	29
3.5	8	9	10	12	14	16	19
4.0	5	6	7	8	9	10	12
Non-diabetic patients							
2.5	11	13	15	18	21	24	28
3.0	7	8	10	11	13	15	18
3.5	5	5	6	7	9	10	12
4.0	3	4	4	5	6	6	7

question. It is also premature to conclude if there is difference between sirolimus versus paclitexel-based DES in late stent thrombosis and whether newer generations of DES with different metallic and/or polymer components may behave differently. Further prospective controlled trials with a clear definition of stent thrombosis will be needed to confirm or disprove the risk of late stent thrombosis.

References

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