

Risk profiling patients for selective use of drug-eluting stents is warranted

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Drug-eluting stents (DESs) have revolutionized the world of interventional cardiology. In many countries worldwide, DESs account for approximately 80% of all stents implanted.¹ When compared with other technologies, such as implantable cardioverter-defibrillators, the adoption of DESs into mainstream clinical practice has occurred more rapidly and without the same rigorous scientific evaluation in important subgroups. While DESs might have slain the Goliath of restenosis, late stent thrombosis (LST) and bleeding associated with prolonged dual antiplatelet therapy used to prevent LST, have created a delicate risk–benefit equation that is only now coming to light. Current views on how to manage this quandary range from dismissing the LST phenomenon as unimportant and continuing with the unrestricted use of DESs, to a panic reaction that would result in a substantial reduction in DES use. Instead of polarizing to either of these extremes, we believe there is a need for a strategy that evaluates the risk–benefit ratio for individual patients.

The LST controversy first became evident with the presentation of the 1-year outcomes of the BASKET-LATE study² at the ACC Annual meeting in March 2006. The results of this trial showed that patients in the DES arm suffered higher rates of mortality and myocardial infarction (MI) than those in the bare-metal stent (BMS) arm. This increase in event rates was largely attributable to LST (DES 2.6% vs BMS 1.3%).² The debate gathered strength at the World Congress of Cardiology in September 2006, where published data from a large, two-center DES registry, showing that the incidence of LST was 0.6% per year, were presented.³ Furthermore, two recent meta-analyses of trials comparing DESs with BMSs both revealed that DES patients had higher late mortality.^{4,5} In December 2006, an FDA panel was convened to review all evidence pertinent to this controversy.⁶ In March 2007, the *New England Journal of Medicine* published five studies (featured in the Research Highlights section of this issue of

Nature Clinical Practice Cardiovascular Medicine) presented at the FDA meeting, which further fuelled the DES debate. The Swedish SCAAR registry⁷ provided data on 19,771 patients (DESs $n=6,033$ and BMSs $n=13,738$) showing that patients in the DES arm experienced higher 3-year mortality (adjusted relative risk 1.18) than those with BMSs. The four pooled analyses of patient-level data, however, concluded that there was no significant difference in the rates of death and MI between patients with DESs and BMSs at 4 years, although there was evidence of increased LST 1–4 years after stent implantation.^{1,8–10} The FDA panel concluded that when DESs are used for approved indications the risk of thrombosis does not outweigh the benefits in terms of reduction in repeat revascularization rates. The panel did, however, warn that the off-label use of DESs was associated with increased death, MI, and LST.⁶ These data caused physicians who refer patients for revascularization procedures to individualize therapy rather than adhering to a guideline-driven approach.

Whenever a new therapy is introduced, initial small studies tend to exaggerate the magnitude of the benefit or harm. Subsequent large, randomized trials are generally underpowered to recognize rare adverse events. Later, meta-analyses of multiple trials and observational studies afford us the opportunity to evaluate the safety of interventions in larger numbers of patients. Ultimately, we might never know the true risk of an intervention until many years after the therapy has been approved. The emerging evidence in the cyclo-oxygenase 2 inhibitors controversy evolved along these lines. The cyclo-oxygenase 2 story also highlights the dangers of initially evaluating new therapies in low-risk groups. Most therapies with established safety and efficacy in cardiovascular medicine, such as implantable cardioverter-defibrillators, angiotensin-converting-enzyme inhibitors, statins, and β -blockers were initially tested in high-risk populations before expanding their use to lower-risk groups. By contrast, DESs were

evaluated and approved in lower-risk populations, but are routinely being used off-label in higher-risk populations.

Risk profiling patients who undergo percutaneous coronary intervention (PCI) is warranted given the totality of evidence comparing BMSs with DESs. High-risk patients, such as those with diabetes, are not only the most likely to benefit from DES implantation, but also the most likely to experience LST. Furthermore, the BASKET trial¹¹ showed that the widespread adoption of a DES strategy was not as cost-effective as adoption in selected patient populations. On the basis of patient and lesion characteristics, a risk–benefit prediction score for DESs that would weigh the cumulative risk of LST, and the concomitant bleeding associated with prolonged dual antiplatelet therapy, with the benefit of reducing target vessel revascularization, is needed. Emphasis should be placed on the importance of aggressive risk-factor modification as frontline therapy for coronary disease. Data from the National Health and Nutrition Examination Survey shows that diabetes is only optimally managed in about 10% of patients.¹² Adherence to a medical program could be the best indicator of compliance with dual antiplatelet therapy after PCI with DESs.

The FDA Advisory Panel, in agreement with the ACC/AHA/ Society for Cardiac Angiography and Interventions (SCAI) PCI Practice Guidelines, recommends 3–6 months of dual antiplatelet therapy for patients undergoing PCI with DESs, while encouraging 9–12 months of therapy for those at low-risk for bleeding.⁶ A report from SCAI cautions interventionalists to pay close attention to stent selection and implantation techniques, to assess the potential compliance of the patient with regards to prolonged dual antiplatelet therapy before stent implantation, and to stress to the patient the need for a discussion of the risks and benefits before discontinuing antiplatelet therapy because of cost or a noncardiac procedure.¹³ In the near future, bioabsorbable stents or the use of bone marrow cells to promote endothelialization could reduce stent thrombosis, while maintaining the benefit of reduced rates of repeat revascularization. In addition, sophisticated imaging modalities to evaluate stent endothelialization could help guide the optimum duration of dual antiplatelet therapy.

The apprehension about DES-related LST is justified and should be addressed in well-designed, prospective studies. There is a need to better define the complex balance between in-stent restenosis, LST, and bleeding, in terms of their relationship to cardiovascular events. In the attempt to win the battle against restenosis, have we lost the war against major cardiovascular events? Now is the time to reflect and reevaluate the appropriate role of DESs in our therapeutic arsenal for fighting coronary disease.

Competing interests

The authors declared they have no competing interests.

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