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Drug-eluting stents and late outcomes

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Despite rapid advances in the applicability and safety of coronary angioplasty over its first quarter century of existence, restenosis following initially successful revascularisation remained a seemingly insoluble limitation of the procedure. Given the long-standing frustration associated with lesion recurrence, the dramatic reductions in restenosis recently brought about by drug-eluting stents (DES) have been met with unconcealed enthusiasm among interventional cardiologists. Despite the lack of long-term outcome data, DES has been rapidly adopted into clinical practice, often for clinical indications and lesion subsets exceeding those tested in the clinical trials. In spite of their cost (approximately triple that of bare metal stents), over 90% of coronary stents used in many hospitals are DES, with the result that in only a few years DES have been implanted in an estimated 6 million individuals worldwide, with total sales exceeding 5 billion US dollars per year.

While the short-term effectiveness of DES for preventing restenosis remains indisputable, three separate studies presented at the recent World Congress of Cardiology in Barcelona with follow-up extending up to 4 years have raised unexpected concerns regarding the long-term safety of the currently available first-generation sirolimus and paclitaxel-eluting stents. These studies, two of which represented meta-analyses of randomised DES trials and the third an examination of a large DES registry, suggested that the short-term restenosis benefits of currently available DES might be counterbalanced by an increased likelihood of more clinically devastating late events such as stent-thrombosis, myocardial infarction, and perhaps cardiac and even non-cardiac mortality.

From a mechanistic perspective, these results lend support to the contention that DES may be so effective in inhibiting stent endothelialisation and neointimal hyperplasia formation that they leave the stent vulnerable to thrombosis for months or possibly even years following implantation, necessitating prolonged or perhaps indefinite dual anti-platelet therapy with aspirin and a thienopyridine. Within the DES registry study presented in Barcelona, late thrombosis continued to occur in a linear fashion at a rate of 0.6% per year throughout the three-year study period, without evidence of levelling-off at 3 years. Moreover, 77% of stent thrombosis episodes occurred among patients not on dual anti-platelet therapy at the time of the event.

Given the potential concerns raised by these findings, should our current practices regarding DES implantation be altered and, if so, how? Clearly, prospective long-term follow-up studies of various DES platforms, drugs types and release kinetics need to be performed to better understand the true incidence of late thrombosis and the effects of these parameters on thrombosis rates. Subgroup analyses should be undertaken to better understand what lesion types, procedural variables and patient co-morbidities predict better or worse long-term outcomes following DES. Studies to determine the optimal duration of dual anti-platelet therapy following DES implantation are essential. In addition, a better understanding is needed of the mechanism by which late thrombosis (and possibly even excess late non-cardiac mortality) occurs after DES placement. Because this information will, however, take years to accumulate, we are left with the issue of how to treat patients today.

Pending further data, the following principles regarding the selection of patients for DES seem reasonable:

— DES placement should be limited to clinical scenarios and lesion subsets with proven

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indications. Prudence would dictate avoiding techniques that are known to be associated with higher rates of stent thrombosis, such as many forms of bifurcation DES placement. Likewise, the temptation should be strictly avoided to place a DES at the site of an angiographically moderate stenosis that is not proven to be flow-limiting, which may be enticing to some interventionalists because of the low likelihood of restenosis;

— impeccable stent implantation technique, including proper stent sizing and expansion relative to the true vessel diameter, is obligatory and may play a role in reducing thrombosis risk. Limiting total stent length to that of the lesion length may also reduce the propensity for late stent thrombosis;

— for patients in whom prolonged (or possibly indefinite) dual anti-platelet therapy is potentially not safe or desirable, DES should probably be avoided. This may include individuals requiring chronic warfarin therapy, those with increased bleeding risk or prior major haemorrhagic events, and those who require non-cardiac surgery necessitating discontinuation of anti-platelet therapy within the next year;

— DES use should probably also be avoided among individuals with a high potential for non-compliance with their anti-platelet therapy.

While drug-eluting stents have revolutionised the practice of interventional cardiology in a very short period of time, the concerns raised regarding late thrombosis must be considered real. More data is needed regarding the true incidence, timing, and clinical sequelae of late events following DES placement. As time progresses, the issue of late thrombosis will be better understood and, it must be hoped, can be overcome by modifications to the DES design. In the meantime, prudent use and careful weighing up of the risks and benefits of DES implantation to individual patients is warranted.