Are drug-eluting stents living up to the hype?

Adrian P Banning

Drug-eluting stents (DES) have been available commercially in the UK for over three years. The National Institute for Clinical Excellence (NICE) produced a technology appraisal in October 2003[1] and that initial review is about to be updated. Well, has this technology delivered on its promise? Have we embraced it too quickly or is 100% DES usage around the corner?

The report in this edition of the journal gives us an insight into our current clinical practice.[2] The Southampton unit is probably the front runner in DES usage in the UK and during the period April 2002–September 2003 they implanted DES in 50% of their patients. In 75% of these cases the decision to use DES was considered to be in line with NICE guidelines but, in 25%, DES usage was outside the guideline and could be considered 'off label'. A third (33%) of patients who should have received DES received a bare metal stent instead. Drs Wells and Dawkins conclude that the NICE estimate of one third DES usage is a significant underestimate. They estimate that three quarters of our percutaneous coronary intervention (PCI) population should already be receiving DES based on the current NICE recommendation.

When we look at the NICE guidance we must remember that it was produced three years ago, at a time when all we really knew was that DES were more effective than bare metal stents for treating relatively simple areas of atheromatous disease. Over an intermediate time window, they appeared to be safe and there was probably no 'catch up' restenosis at the completion of the drug elution. The NICE recommendations were based on lesion characteristics alone, partly because there were very few data on specific patient characteristics like diabetes.

In retrospect, it was perhaps surprising that in this relatively straightforward patient subset such dramatic differences between DES and bare metal could be demonstrated. It is beyond the scope of this article to review and reference all the DES data published and presented since then, but clearly we have moved on! Randomised trials and registry data have shown benefits from DES in diabetics, long lesions and in-stent restenosis,[3-10] and there are increasing data in bifurcations, primary angioplasty and left main disease.

Looking at this list, perhaps it is easier to consider which patients shouldn't get DES? When one takes an overview of the available data, the considerable benefits of DES are apparent – the principal remaining issue is possible safety concerns as, ultimately, any problems with stent delivery will be surmounted. The *Lancet* report in 2004[11] from the Thorax Center of four patients with very late thrombosis after discontinuation of all antiplatelet medications resounded around the world. It was meat and drink to the sceptics and to those device companies who didn't yet have their own DES.

A more recent report in *JAMA* from Colombo's Milan group reports a 1.3% rate of drug-eluting stent thrombosis (nine [0.8%] with sirolimus and 20 [1.7%] with paclitaxel; p=0.09) and concludes that premature antiplatelet therapy discontinuation, renal failure, bifurcation lesions, diabetes, and low ejection fraction identify patients at risk.[12] Fourteen patients had subacute thrombosis (0.6%) and 15 patients had late thrombosis (0.7%). Among these 29 patients, 13 died (case fatality rate, 45%). The mortality rate, particularly, is noteworthy.

Early and late thrombosis issues

In my opinion, these data on early thrombosis are not particularly surprising or alarming. They show that challenging patient subsets are being treated with DES and remind us of the lessons learnt in the past about how to deploy stents safely. We must be committed to complete stent expansion even in calcific disease, full lesion coverage, ensuring that bifurca-

tions have no struts prolapsing in the lumen and careful and appropriate use of antiplatelet therapy. Glycoprotein IIb/IIIa inhibitors should not be discarded too quickly in difficult patient subsets.

The incidence of late thrombosis is harder to explain away. It is possible that the mechanism of late thrombosis is similar to early thrombosis and related to delayed re-endothelialisation of less well expanded stents, but there are other possibilities. Both hypersensitivity reaction to the polymer and potentially harmful effects of a lingering drug reservoir have been suggested. Inherent patient-related factors are also a possibility. One could speculate that in view of these data, we should avoid using DES in these high-risk patients – but it is these same patients who are most likely to gain from the technology.

I think we must recognise that DES technology has clearly allowed PCI to advance and that interventionalists around the world are treating more and more complex disease in patients with higher risk. Clinical practice is ahead of the trial data and many higher risk patients have already been receiving DES without definitive evidence of the efficacy and safety of DES for that lesion or that patient. Should we be concerned about this? Well, we need to be mindful of the situation. Vigilant monitoring and a robust national reporting system with standardised definitions are urgently required. But with so many stents implanted and so few reported events, turning back the DES tide is unlikely. We must remember what an extraordinary and enormous step forward DES technology is, and that there really have been remarkably few problems. It is easy for us to forget the years of fruitless research in the 1980s and '90s into prevention of balloon angioplasty restenosis. DES technology is probably a larger step forward than the initial data that prompted stent-mania in the mid-90s.

The future

And what of the future? Simultaneous improvements in stent design, particularly in stent deliverability, will occur. There will be multiple drug combinations perhaps including both antithrombotic and antiproliferative agents with differential rates of release, and newer more potent agents will arrive, perhaps encompassing strategies that will encourage quicker re-endothelialisation. Stent lengths will continue to increase, as there is a need to cover all the atheroma and increasing numbers of bifurcations will be covered/treated. Increased competition, resulting in lower prices, will ensure the dominance of DES in the future.

Ultimately, drug-eluting stents will shift the time of intervention to an earlier point in the disease process. Intermediate stenosis will be treated with drug-eluting stents and immediate revascularisation will soon become mandatory for all patients presenting with manifestations of ischaemic heart disease. Comparisons with bare metal stents are already probably unethical and alternative trial designs will be necessary. In our field perhaps more than any other, experimental results are widely publicised before formal peer-review has been completed. This practice is inevitable in a market place with such rich financial reward and where such intense speculation about results occurs. The integrity of the independent trial management consultants, core radiographic and IVUS laboratories, and the interventional cardiology industry as a whole, is essential to maintain a core standard of randomised data which is the envy of many clinical trial investigators throughout medicine.

Conclusion

So, will there be DES for all? No, in some patients, particularly the frail elderly and patients scheduled for non-cardiac surgery etc., DES with obligatory prolonged dual platelet treatment are not currently the optimal treatment. Bare metal stents remain the best option. For everybody else…….well, in my opinion DES are 'better' than bare metal. We should acknowledge the late thrombosis issue and be vigilant, but DES will not go away and bare metal stents will soon comprise a tiny minority of our interventional practice.

Conflict of interest

Dr Banning was an investigator in the Taxus II and Taxus VI studies. He has received research funding from Boston Scientific.

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