Cost-effectiveness of drug-eluting stents: if only all things were equal

They reduce rates of restenosis but not mortality or infarction — so are they worth it?

The development of drug-eluting coronary stents has proven to be a quantum advance in interventional cardiology, rivalling the impact of stenting itself. Drug-eluting coronary stents deliver effective local concentrations of antiproliferative drugs (thus avoiding systemic toxicities), without substantially modifying the technique of percutaneous coronary intervention (PCI). Two of the drugs used are sirolimus and paclitaxel. Sirolimus is an inhibitor of the G1-phase of the cell cycle, while paclitaxel inhibits microtubule formation, both of which are necessary for cell division. Thus, they inhibit the natural healing mechanisms — endothelial cell migration and extracellular matrix formation — that produce intimal hyperplasia, resulting in restenosis.

Randomised clinical trials of patients with stents that elute these agents have demonstrated reduced angiographic restenosis rates when compared with patients with bare-metal stents.[1,2] These individual trials are supported by a recent meta-analysis of 11 randomised clinical trials involving 5103 patients; this showed that, in patients with drug-eluting stents (compared with those receiving bare-metal stents), there was a significant reduction in the proportion of patients requiring target lesion revascularisation (Box).[3] Thus, within the context of randomised trials, and when all other things are equal, drug-eluting stents are clearly superior in preventing restenosis, which is the most significant late morbidity associated with coronary intervention.

But, not all things are equal — these stents come at an approximately threefold increase in economic cost.

As a consequence of this cost differential, the benefits of this new technology need to be considered critically. While the meta-analysis confirmed that drug-eluting stents decrease rates of restenosis and target lesion revascularisation,[3] there was no evidence that they reduced deaths and myocardial infarction rates. However, given the nature of the innovation, this would not be expected. Furthermore, from the patient's perspective, the impact of drug-eluting stents on the more relevant endpoint of "any" coronary revascularisation (as opposed to "target lesion" revascularisation) has not been highlighted and will be eroded by the development of *de novo* disease in other areas of the coronary vasculature.[6]

Among cardiologists and patients, this technology has been embraced with substantial enthusiasm. Drug-eluting stents are now being implanted in patients in subgroups and with lesion types beyond those evaluated by randomised trials.[7] Some clinicians have also proposed that multi-vessel PCI using drug-eluting stents provides a comparable alternative to coronary artery bypass grafting.[8] This preference is best illustrated by the disparate rates of drug-eluting stent implantation in the private and public sectors, estimated at >75% and <25%, respectively, reflecting the difference in who is paying for this technology.

Several issues make it difficult to compare the cost-effectiveness of the two types of stents. First, without a benefit in terms of mortality, assessment of cost-effectiveness by cost-per-life-year saved is precluded. To circumvent this issue, a published cost-effectiveness analysis from the SIRIUS trial of sirolimus-eluting stents in elective PCI used quality-adjusted life-year (QALY) data drawn from a trial of bare-metal stenting for reperfusion therapy after myocardial infarction.[4] Whether these QALY data are applicable to the patients in the SIRIUS trial, and to Australian patients, is uncertain. Given the potential lack of generalisability of clinical trial data to clinical practice, the use of QALY data from patients

Summary of evidence related to drug-eluting stents

- A Bayesian meta-analysis* of 11 randomised controlled trials comparing drug-eluting stents with bare-metal stenting[3] showed the former had:
  - — No effect on mortality rates (odds ratio, 1.11; 95% credible interval*, 0.61–2.06)[3]
  - — No effect on rates of myocardial infarction (odds ratio, 0.92; 95% credible interval*, 0.66–1.25)[3]
  - — Substantially lower rates of target lesion revascularisation (odds ratio, 0.26; 95% credible interval*, 0.14–0.45)[3]
  - — Fewer major adverse cardiac events when death, myocardial infarction, and target vessel revascularisation are combined (odds ratio, 0.42; 95% credible interval*, 0.32–0.53)[3]
- In a randomised comparison of sirolimus-eluting versus bare-metal stents in elective percutaneous coronary intervention, the incremental cost-effectiveness ratio was estimated to be US$27 540 per quality-adjusted life-year gained.[4] This reflects the money that needs to be spent to gain a benefit of one quality-adjusted life-year with this technology.
- Up to 50% of patients undergoing percutaneous coronary intervention have characteristics that would have led to their exclusion from clinical trials of drug-eluting stents in the US Dynamic Registry, a comprehensive angioplasty registry sponsored by the National Heart, Lung and Blood Institute.[5]

*In a Bayesian meta-analysis, "credible interval" corresponds to confidence interval.

treated within a different clinical context may lead to a cost-effectiveness extrapolation not relevant to our local context.

The time has come for the Australian cardiology community to develop national systems that routinely assess the long-term clinical outcomes of all patients undergoing PCI and coronary artery bypass grafting. Such data should yield several benefits. First, actual local data on effectiveness are essential for locally relevant cost-effectiveness estimates. Second, data on specific patient and lesion subsets inadequately studied in randomised trials will allow us to apply this innovation to patients most likely to benefit from it.[9] Such data are vital to the rational development of practice guidelines and reimbursement strategies for optimal patient outcomes and health care expenditure. Third, as with any emerging therapy or technology, routine evaluation of long-term safety remains a priority; this has been highlighted by the recent report of very late stent thrombosis associated with drug-eluting stents.[10] Routine systems of evaluation would provide an effective infrastructure for surveillance of unexpected adverse events occurring after a new technology has been approved, and would be less reliant on physicians for recognition and reporting.

Problems relating to the costs of data collection and the difficulties of risk adjustment remain to be solved before nationwide registries can be implemented. However, the clinical and economic consequences of inappropriate application of this and other technologies would exceed these costs, potentially by orders of magnitude. The resource burden associated with assessing implementation of a new technology should not be used as an argument against its conduct, but rather should encourage the incorporation of this activity into routine clinical practice and funding.

It has been argued that, with time, the cost of drug-eluting stents will fall, clinical experience will grow, and the application of this technology to clinical practice will be optimised.[11] Over the past 10 years, the cost of bare-metal stents has declined by approximately 60%. Yet, interventional practice remains heterogeneous, and outcomes remain uncertain. Registries designed to assess practice, outcomes and cost will offer essential objective data to inform rational choices — until the time when all things become equal.

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