

Are drug-eluting stents safe in the long term?

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∞ See related research paper by Philpott and colleagues, page 167

The use of drug-eluting stents has become widespread globally. However, in the last 2 years concerns have been raised regarding their long-term safety.^{1,2} Recent registry studies and meta-analyses seem to have provided reassuring results about the long-term rates of death and myocardial infarction associated with the use of drug-eluting stents compared with bare-metal stents.³⁻⁵ However, concerns remain, especially regarding the risk of late (beyond 30 days) and very late (beyond 1 year) stent thrombosis. The cause, pathophysiology and timing of late and very late thrombosis are not fully understood.

In this issue of *CMAJ*, Philpott and colleagues report the results of their 3-year study of data from a prospective multi-centre registry.⁶ They compared rates of death and of the combined outcome of death or repeat revascularization among 6440 consecutive patients who underwent angioplasty with either bare-metal or drug-eluting stents. As expected, drug-eluting stents were used more often than bare-metal stents in patients with comorbidities that placed them at increased risk of restenosis and thrombosis (e.g., diabetes mellitus and renal disease) or with high-risk lesions (e.g., longer lesions, smaller vessels, stenosis of the left main coronary artery). Compared with bare-metal stents, drug-eluting stents were associated with a lower mortality and a lower combined rate of death or repeat revascularization at 1 year.

These findings are concordant with results from randomized controlled trials and observational studies. Recent pooled analyses of randomized trials with up to 4 years of follow-up showed significant reductions in the rates of revascularization of target lesions and other restenosis-related outcomes associated with drug-eluting stents compared with bare-metal stents. However, these studies found no significant difference in the rates of death or myocardial infarction.^{3,5} In contrast, greater reductions in all-cause mortality, by up to 20%, with drug-eluting stents than with bare-metal stents have been shown in observational studies, such as the one by Tu and colleagues.⁷ In a recent, large observational study, Mauri and colleagues⁸ conducted an analysis of matched propensity scores. They reported significant differences in both 2-year mortality and risk of myocardial infarction in favour of drug-eluting stents among patient presenting with acute myocardial infarction. Furthermore, a recent large meta-analysis of 34 observational studies including more than 180 000 patients showed that drug-eluting stents were associated with signifi-

Key points

- Drug-eluting stents are associated with significant long-term reductions in repeat revascularization, restenosis and target-vessel revascularization compared with bare-metal stents. They may also be associated with decreased mortality.
- The long-term safety of drug-eluting stents, especially regarding late and very late thrombosis, remains a concern.
- The optimal duration of dual antiplatelet therapy in patients with drug-eluting stents remains unknown.

cant reductions in rates of death, myocardial infarction and revascularization of target vessels.⁹ However, these observations should be considered only as hypothesis generating, since observational studies, despite the use of analyses of matched propensity scores, are unable to correct entirely for unmeasured confounders.

The long-term benefit of drug-eluting stents for reducing restenosis-related outcomes is well established. However, in the study by Philpott and colleagues, their sensitivity analysis of matched propensity scores showed that, although the survival benefit at 1 year with drug-eluting stents relative to bare-metal stents remained (mortality 2.7% v. 4.3%, $p = 0.043$), the difference in the combined outcome of death or repeat revascularization was not significant between the 2 groups (11.7% v. 12.7%, $p = 0.46$). This finding suggests either a lack of power, uncontrolled selection bias or unmeasured confounding.

Another important finding of their study is the temporal change in outcomes over the 3-year follow-up period. After 240 days, the advantages of drug-eluting stents decreased, and a nonsignificant trend suggested a worse outcome compared with bare-metal stents. This finding is reminiscent of the large cohort study by Daemon and colleagues.² They found that, despite antiplatelet therapy, late stent thrombosis occurred unpredictably at a constant rate of 0.6% per year up to 3 years after stent implantation. Also, in a large meta-analysis of 36 trials involving 18 023 patients, Stettler and colleagues¹⁰ observed a late temporal trend at 4 years that suggested a lower incidence of stent thrombosis with bare-metal stents than with drug-eluting stents.

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Multiple reasons other than late or very late thrombosis could explain this temporal change in outcomes with drug-eluting stents. As Philpott and colleagues report, the patients who received drug-eluting stents were at much higher risk of restenosis and stent thrombosis than those given bare-metal stents. Even if the authors had controlled for some potential confounding variables in their sensitivity analysis of matched propensity scores, other uncontrolled variables may have influenced the outcomes. Use of medications (e.g., acetylsalicylic acid, clopidogrel, angiotensin-converting-enzyme inhibitors, statins, β -blockers and angiotensin II receptor blockers), use of intravascular ultrasound during percutaneous coronary intervention and bleeding after the procedure are well known to affect the long-term prognosis. They were not measured in the present study. Thus, an increased incidence of late or very late stent thrombosis may reflect the natural history of a higher-risk population. In addition, without knowing the rates of revascularization of target vessels or target lesions, there is no way to determine whether revascularization was done because of stent failure or because of progression of the disease in other vessels.

Alternatively, late or very late stent thrombosis may be explained by the discontinuation of dual antiplatelet therapy between 6 and 12 months after stent placement. In a prospective observational cohort study, Iakovou and colleagues¹¹ showed that the strongest independent predictor of stent thrombosis was premature discontinuation of antiplatelet therapy. This may once again raise the issue of the optimal duration of antiplatelet therapy after stent placement, particularly in high-risk patients with high-risk lesions.

The most important question remains: Why have observational studies such as the one by Philpott and colleagues shown a significant decrease in mortality associated with drug-eluting stents compared with bare-metal stents, when randomized controlled trials and meta-analyses of randomized controlled trials have not? One hypothesis is that patients in observational studies who were given stents for “off-label” indications had higher risk characteristics and thus may have been exposed to a longer duration of dual antiplatelet therapy or more optimal medical treatment. This may explain why Philpott and colleagues found significant benefits with drug-eluting stents at 1 year in the subgroup of patients with acute coronary syndromes but not in the group with stable angina. Another hypothesis is that, because drug-eluting stents are associated with lower rates of repeat revascularization and restenosis than bare-metal stents are, fewer patients with drug-eluting stents underwent repeat procedures, which are

themselves associated with morbidity and mortality. Finally, selection bias in observational studies and the inclusion of only low-risk patients with low-risk lesions in randomized controlled trials may have influenced the outcomes of these studies. Therefore, the survival benefit associated with drug-eluting stents relative to bare-metal stents may be either multifactorial or artifactual, depending on the study design.

Despite the large amount of favourable long-term data on the use of drug-eluting stents from randomized controlled trials, meta-analyses and observational studies, the long-term safety of drug-eluting stents, especially regarding late and very late stent thrombosis, remains a major concern. More studies such as the one by Philpott and colleagues are needed to address this unresolved issue.

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