Clinical Research

Time Dependency of Outcomes for Drug-Eluting vs Bare-Metal Stents

Alexander A. Leung, MD, MPH, Danielle A. Southern, MSc, P. Diane Galbraith, RN, BN, Merril L. Knudtson, MD, Andrew C. Philpott, MBBS, and William A. Ghali, MD, MPH, for the APPROACH Investigators

Department of Medicine, University of Calgary, Alberta, Canada
Department of Community Health Sciences, University of Calgary, Alberta, Canada
Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada
Lyell McEwin Hospital, Adelaide, South Australia

ABSTRACT

Background: Previous research suggests that the early benefit from revascularization with drug-eluting stents might diminish over time.

Methods: We performed an extended analysis of a previously identified cohort of 6440 patients who underwent percutaneous coronary intervention between April 1, 2003 and March 31, 2005 using a prospective provincial clinical registry in Alberta, Canada. We compared rates of death, and of death or repeat revascularization among the 6440 patients receiving either drug-eluting (sirolimus- and paclitaxel) stents or bare-metal stents. We determined risk-adjusted hazard ratios at moments in time with a spline analysis using Cox proportional hazards modelling.

Although the use of drug-eluting stents (DESs) has become widespread as the result of trials demonstrating significant reduction in stent restenosis and subsequent repeat revascularization compared with bare-metal stents (BMSs), concerns have been raised regarding the possible increased risk of late complications and mortality with DESs.

Accordingly, we previously reported results from a prospective cohort of patients receiving either DESs or BMSs from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) registry with 3 years of follow-up, and demonstrated an initial suggestion of benefit among patients receiving DESs, followed by a shifting of relative risk over time toward worse outcomes in DES patients for the combined outcome of death or repeat revascularization. Our findings suggested that the pace of occurrence of adverse events among patients receiving DESs was not uniform, and that insufficient follow-up duration might lead to underestimation of late events.

Existing reports of the long-term safety of DESs have been conflicting. Considering the concerns about the safety of DESs, especially with the growing awareness of long-term complications relating to the stent itself and the associated bleeding risk from dual antiplatelet therapy, we present a follow-up analysis with 8-year post-stent data to extend our understanding of whether the use of DESs is associated with a significantly greater long-term risk of death or repeat revascularization compared with BMSs.

Methods

Study design and patient population

A prospective cohort of all patients undergoing percutaneous coronary intervention with BMSs or DESs in the province of Alberta between April 1, 2003 and March 31,
Results: During the 8 years of observation, the relative risks for death or the composite outcome of death or repeat revascularization varied over time. There was an early finding of better outcomes associated with drug-eluting stents in the first year after implantation. Thereafter, there was no significant benefit associated with drug-eluting stents compared with bare-metal stents with 8 years of follow-up. At 30 days, the adjusted hazard ratio was 0.38 (95% confidence interval [CI], 0.18-0.81) for death and 0.27 (95% CI, 0.14-0.54) for the composite outcome of death or repeat revascularization. By 8 years, the adjusted hazard ratio of death or the composite outcome was 1.15 (95% CI, 0.97-1.36) and 1.01 (95% CI, 0.87-1.17), respectively.

Conclusions: Revascularization with first-generation drug-eluting stents is associated with better outcomes within the first year only. Thereafter, the risk of death or repeat revascularization is similar between drug-eluting stents and bare-metal stents.

Outcomes

The main outcome measures were death and the composite of death or repeat revascularization of any coronary vessel. For our present analyses, relinkage of data from the Alberta Bureau of Vital Statistics was performed for ascertainment of death among patients in the cohort. Information on subsequent revascularization (ie, percutaneous coronary intervention or coronary artery bypass graft surgery) was obtained using the APPROACH database. Of note, APPROACH was integrated with the provincial personal health record and was present in all facilities performing revascularization procedures in Alberta, ensuring complete capture of all revascularization attempts during the study interval within the province.

Analysis

Baseline clinical and demographic characteristics of patients with DESs were compared with those with BMSs using the \( \chi^2 \) test for categorical variables and Student t test for continuous variables. To address potential confounding by treatment indication, we used a propensity score and multivariable regression modelling to account for baseline differences between recipients of BMSs and DESs. The propensity score also helped to reduce the dimensionality of the large number of potentially important covariates compared with the relatively few outcomes before modelling to improve parameter estimates. Variables incorporated into the propensity score were selected based on discrimination (determined using the c-statistic) and clinical reasoning (Supplemental Table S1). Continuous variables (eg, ejection fraction, Duke Myocardial Jeopardy score, and stent length) were categorized according to clinically relevant cutoff values as used in previous studies. For our primary analysis, the propensity score was incorporated as a covariate in our regression model. Outcomes were compared for the entire cohort, and for the 2 prespecified subgroups according to the primary indication for catheterization: acute
coronary syndrome (ie, myocardial infarction within 8 weeks of catheterization, or unstable angina), and stable coronary syndrome (ie, stable angina). Follow-up data were complete for all patients for at least 6 years (ie, for those enrolled in the cohort as late as 2005) and for up to 8 years for those enrolled earlier. To visualize the occurrence of events over time, we used Kaplan-Meier survival analysis to compare the crude rates of death and the composite outcome of death or revascularization. After fitting a Cox regression model with our candidate variables, we tested for and found violations to the proportional hazards assumption using Schoenfeld residuals. To address the changing relationship between the exposure and outcome over time, we conducted a risk-adjusted, time-dependent spline analysis using Schoenfeld residuals to determine the relative risk at moments in time (with 95% confidence bands).17-19 This analysis was determined a priori (based on previous work) to address the presence of time-varying covariates.10 Finally, to test the robustness of our findings, we repeated the analysis with a propensity-score matched cohort. All possible pairs were identified with 1:1 matching without replacement using a caliper of 0.01 (on a scale of 0 to 1). All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Of the 6471 patients undergoing percutaneous coronary intervention, 31 patients had balloon angioplasty without stents and were excluded from further analysis. Among the remaining patients, 1120 (17.3%) received DESs, and 5320 (82.2%) received BMSs. The mean age was 62 years and similar between the 2 groups. Patients receiving DESs were more likely to be female, have concomitant renal disease, diabetes mellitus, hyperlipidemia, and hypertension. Those receiving BMSs were significantly more likely to have had a previous myocardial infarction and were more likely to have received stenting for an acute coronary syndrome (Supplemental Table S2). For the cohort of 6440 patients, an early 30-day survival advantage was observed in those receiving DESs compared with BMSs (0.7% vs 1.8% mortality at 30 days; adjusted hazard ratio [HR], 0.38; 95% confidence interval [CI], 0.18-0.81). Thereafter, mortality rates between the 2 groups became more similar and were not significantly different at 6 years after catheterization (13.2% vs 12.4% mortality at 6 years; adjusted HR, 1.04; 95% CI, 0.86-1.26). Similarly, the initial risk of the composite outcome of death or repeat revascularization was higher among BMS recipients (4.1% vs 6.1% for DESs and BMSs, respectively; adjusted HR, 0.27; 95% CI, 0.14-0.54). By 6 years, DESs were associated with more adverse events for the composite outcome (31.3% vs 29.8% for DESs and BMSs, respectively; adjusted HR, 0.96; 95% CI, 0.82-1.13). Among the subgroup of patients with stable coronary syndromes, no difference in survival between the 2 intervention arms was detected during the entire length of the study. Otherwise, the general findings from the subgroup analyses for patients with acute coronary syndromes and stable coronary syndromes were broadly similar to those observed in the total cohort (Supplemental Table S3).

Kaplan-Meier analyses

Unadjusted time-to-event analyses were performed among patients receiving DESs compared with BMSs (Fig. 1). Over the 8-year study period, recipients of BMSs appeared to have a lower mortality rate, but not meeting statistical significance (17.3% vs 16.6%, at 8 years; P = 0.32 for the entire 8 years of follow-up; Fig. 1A). The survival curves for patients with acute coronary syndromes (Fig. 1B) and stable coronary conditions (Fig. 1C) were likewise similar. On examining the overall event-free survival for the composite outcome among patients with
DESs vs BMSs, we observed a similar pattern (36.9% vs 35.3%; \( P = 0.43 \)) (Fig. 2). There was no significant difference in event-free survival for the composite outcome between the 2 intervention arms over time in either subgroup.

**Time-dependent spline analyses**

Figure 3 presents the findings of our time-dependent spline analyses that display the dynamic nature over time of the relative risks for DESs compared with BMSs. These analyses present plots of relative risks at moments in time. Bands (representing 95% CIs) are presented to inform judgements of statistical significance over time. After adjustment for baseline risk factors, the time-dependent spline analysis confirms an initial survival benefit with DESs followed by a transition toward similar outcomes between DESs and BMSs after the first year of intervention (Fig. 3A). This later relationship persisted during the 8 years of follow-up. The adjusted relative risk of death associated with DESs compared with BMSs was 0.38 (95% CI, 0.18-0.81) early in the first year, and then rose to 1.15 (95% CI, 0.97-1.36) at 8 years. Likewise, the analysis of the combined outcome of death or repeat revascularization showed a similar pattern (Fig. 3B). Although outcomes were initially better with DESs, this early benefit attenuated within the first year of treatment. The adjusted relative risk for the composite outcome of death or repeat revascularization was 0.27 (95% CI, 0.14-0.54) early in the first year; by 8 years, the adjusted risk was 1.01 (95% CI, 0.87-1.17).

**Propensity-score matching**

We then repeated the analysis with a propensity-score matched cohort of 1065 matched pairs (Supplemental Table S4). Baseline characteristics between the 2 groups were well balanced with a similar mean age, sex distribution, and prevalence of significant comorbidities; left ventricular ejection fractions, affected coronary territories, and severity scores were also comparable. The results of the adjusted analysis were similar to those of the main analysis (Supplemental Table S5 and Supplemental Fig. S1).

**Discussion**

To our knowledge, this is the first report of 8 years of follow-up data comparing outcomes between DESs and BMSs in an unselected population-based cohort. The benefits of DESs were most clear within the first year of stent implantation, but these early benefits attenuated over time. Reassuringly, however, we did not detect any significant difference in mortality risk associated with first-generation DESs over the 8-year study period.

Our study extends the findings from previous reports. Although there is compelling evidence to show that DESs reduce rates of target vessel revascularization compared with BMSs,\textsuperscript{4,5,20,21} there is debate as to whether DESs are associated with important mortality differences. Indeed, reports of long-term survival and safety with DESs have been conflicting, with some reports raising concerns regarding increased mortality,\textsuperscript{9,22} and others suggesting no mortality difference,\textsuperscript{5,20,22-31} or even decreased mortality.\textsuperscript{32-35} It has been noted, however, that although randomized trials have failed to detect any significant differences in mortality, many observational studies have reported the presence of survival benefit associated with DESs, at least early-on.\textsuperscript{24,36} There might be several explanations for these variable reports: first, unmeasured confounding and selection bias cannot be excluded from nonexperimental designs; second, most studies have only reported outcomes up to 3 years after stent implantation; third, some studies have included patients with multiple coronary lesions, which may dilute the survival advantage of DESs. It is possible that the survival benefit associated with DESs may persist in selected populations, such as those with acute coronary syndromes.

---

**Figure 2.** Unadjusted time to composite outcome (death or revascularization) extending to 8 years among patients with drug-eluting stents (DESs) and those with bare-metal stents (BMSs). (A) All patients (n = 2130); (B) patients with acute coronary syndromes (n = 1347); (C) Patients with non-acute coronary syndromes (n = 783).
repeat revascularization might reflect disease not related to stents, because percutaneous coronary intervention does not alter the natural history of progressive and diffuse atherosclerotic disease in nonstented vessels. For instance, in 1 study, approximately 50% of interventions after DES placement were for lesions outside of the previously stented segment. As such, late events might be a product of disease severity rather than device failure.

Overall, our study suggests that the use of first-generation DESs is safe in the long-term, but is not superior to treatment with BMSs. The principal advantage of using DESs is the reduction of subsequent revascularization. To date, a reduction in the rate of target vessel revascularization is the only evidence-based benefit of DESs. Even so, there has been criticism that the current application of DESs in mainstream practice is not value-based, because these stents are broadly applied even to those at low risk for restenosis, and there is little evidence to demonstrate the superiority of DESs over BMSs outside of highly specific settings. Furthermore, it should be recognized that DESs might not be benign devices. Complications arising from DESs have been well documented. After stent deployment, device-related complications appear to occur at a steady background rate (eg, 3.5% annual rate of target vessel revascularization and 0.6% annual rate of stent thrombosis). Moreover, dual antiplatelet therapy, routinely prescribed for these patients, is associated with significant bleeding risk. Complicating matters even more, the optimal length of therapy has not been established; further extending the use of dual antiplatelet therapy might not be protective, but possibly harmful.

Despite the strengths of our study (ie, a population-based cohort study with complete capture of all deaths and revascularization procedures within the province, and little loss to follow-up because of emigration), there are some limitations. The main limitation is that this is not a randomized trial, and consequently subject to potential confounding. We used propensity score matching and multivariable adjustment as strategies to account for baseline differences between patients receiving either stent type. Although we performed careful statistical adjustments with a large number of potential confounders in all of our outcome analyses to account for differences in disease severity between groups, residual confounding cannot be excluded, particularly in light of the 30-day mortality differences in our study, a finding not reported in previous randomized studies. However, although there are inherent limitations of a nonrandomized registry study, these same study attributes can also be construed as strengths, because they provide real-world outcome data that reflect practice patterns not otherwise captured by highly-selective randomized trials. Second, we did not have data on long-term medication use or the specific anticoagulation regimen administered to patients. However, dual antiplatelet therapy after stent placement was ubiquitous in the jurisdiction studied, in keeping with practice guidelines. At the time of the study, the general provincial policy was to provide dual antiplatelet therapy for a minimum of 9 months for DESs and 3 months for BMSs, with many favouring even longer treatment durations based on published recommendations. However, recent evidence suggests that shorter regimens might be acceptable, and brief interruptions in dual antiplatelet therapy within the first year of intervention might

implantation, and insufficient follow-up duration might lead to underestimation of late events; finally, as we demonstrated, outcomes between DESs and BMSs vary over time. Consequently, studies that do not account for the time-varying relationship in their analyses might miss important mortality differences. In favour of this reasoning, a recent landmark analysis also demonstrated that there was a short-term mortality benefit associated with DESs, but this difference disappeared after 9 months. We likewise confirm these findings and further demonstrate that this pattern persists over 8 years of follow-up, even after adjustment for important clinical confounders.

The variable risk of death and other adverse events associated with DESs and BMSs might relate to the devices themselves, differences in baseline patient characteristics, duration of dual antiplatelet therapy, or a combination of these factors. Some, however, have suggested that the risk of adverse cardiac events is most closely related to the severity of underlying disease rather than stent type. Further, death or

Figure 3. Risk-adjusted spline analysis extending to 8 years of the relative risk of death (A) and the composite outcome of death or revascularization (B) among patients with drug-eluting stents (vs those with bare-metal stents). A relative risk < 1.0 indicates a decreased risk of events among patients with drug-eluting stents. The thin lines above and below the thicker line represent 95% confidence intervals.

(A) Death

(B) Death or Repeat Revascularization

<table>
<thead>
<tr>
<th>Time since intervention, years</th>
<th>Death</th>
<th>Death or Repeat Revascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>7</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>8</td>
<td>0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>
confer minimal clinical risk.\textsuperscript{45,46} The lack of data on medication use, therefore, is unlikely to explain the early differences in mortality or long-term outcomes that we observed. Third, we measured all-cause mortality and did not have data on cardiovascular death. Accordingly, mortality might be related to cardiovascular causes, bleeding complications, and even events unrelated to stent placement. Finally, we reported long-term outcomes associated with first-generation DESs. Although our findings might not necessarily be generalizable to the newer generation of stents in current use, our study nonetheless provides important prognostic information for surviving recipients of older devices.

In conclusion, we were able to quantify the risk of late complications (ie, death or repeat revascularization) associated with first-generation DES placement with up to 8 years of follow-up. The benefits associated with DESs are most appreciable within the first year of treatment. Thereafter, there was no detectable difference in outcomes. The implication of our study is that although first-generation DESs appear to be safe in the long-term, they are not superior to BMSs. There is no convincing evidence that DESs change the long-term risk of mortality or repeat revascularization. Consequently, the widespread “off-label” use of DESs outside of highly specific settings is questionable, particularly because of the unfavourable cost-benefit tradeoff considering the modest effect on short-term survival and negligible differences in long-term revascularization rates.\textsuperscript{38-41} The use of DESs, therefore, should be judiciously reserved for patients at highest risk of target vessel restenosis.

Acknowledgements

The authors gratefully acknowledge the cardiac care personnel in the study hospitals for their diligence in data collection and entry: Foothills Medical Center, Royal Alexandra Hospital, and University of Alberta Hospital. Members of the APPROACH Clinical Steering Committee: Edmonton - Dr Ross Tsuyuki (Chair), Dr Blair O’Neill, Dr Wayne Tymchak, Dr Michelle Graham, Dr David Ross, and Dr Neil Brass; Calgary - Dr Micheal Curtis, Dr William A. Ghali, Dr Merrill L. Knudtson, Dr Andrew Maitland, Dr Todd Anderson, and Dr Mouhieddin Traboulsi.

Funding Sources

APPROACH was initially funded with a grant from the W. Garfield Weston Foundation. The ongoing operation of this project has been made possible by contributions from the Provincial Wide Services Committee of Alberta Health and Wellness and annual contributions from the Edmonton and Calgary zones of Alberta Health Services, and the Libin Cardiovascular Institute of Alberta and Mazankowski Alberta Heart Institute.

The outcome analyses presented in this report were supported by funding obtained from the Canadian Cardiovascular Outcomes Research Team (CCORT) (see www.ccort.ca), a team grant funded by the Canadian Institutes for Health Research.

Dr Knudtson receives partial support from the Libin Trust Fund. Dr Ghali received funding until recently from the Government of Canada Research Chair in Health Services Research. He is also funded by a Senior Health Scholar award from Alberta Innovates Health Solutions. Dr Leung is supported by a Clinical Fellowship Award from Alberta Innovates Health Solutions and by a Fellowship Award from the Canadian Institutes for Health Research.

Disclosures

The authors have no conflicts of interest to disclose.

References


**Supplementary Material**

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at [www.onlinecjc.ca](http://www.onlinecjc.ca) and at [http://dx.doi.org/10.1016/j.cjca.2013.09.003](http://dx.doi.org/10.1016/j.cjca.2013.09.003).