Long-term outcomes of patients receiving drug-eluting stents

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∞∞ See related commentary by Généreux and Mehran, page 154

Abstract

Background: We sought to establish the long-term safety of drug-eluting stents compared with bare-metal stents in a usual care setting.

Methods: Using data from a prospective multicentre registry, we compared rates of death and of death or repeat revascularization during 3 years of follow-up of 6440 consecutive patients who underwent angioplasty with either drug-eluting or bare-metal stents between Apr. 1, 2003, and Mar. 31, 2006.

Results: Drug-eluting stents were inserted in 1120 patients and bare-metal stents in 5320. The drug-eluting stents were selected for patients who had a greater burden of comorbid illness, including diabetes mellitus (32.8% v. 20.8% in the bare-metal group, $p < 0.001$) and renal disease (7.4% v. 5.0%, $p = 0.001$). At 1-year follow-up, the drug-eluting stents were associated with a mortality of 3.0%, as compared with 3.7% with the bare-metal stents (adjusted odds ratio [OR] 0.62, 95% confidence interval [CI] 0.46–0.83). The rate of the composite outcome of death or repeat revascularization was 12.0% for the drug-eluting stents and 15.8% for the bare-metal stents (adjusted OR 0.40, 95% CI 0.33–0.49). In the subgroup of patients who had acute coronary syndromes, the adjusted OR for this composite outcome was 0.46 (95% CI 0.35–0.61). During the 3 years of observation, the relative risks for death and repeat revascularization varied over time. In year 1, there was an initial period of lower risk in the group with drug-eluting stents than in the group with bare-metal stents; this was followed by a shift toward outcome rates favouring bare-metal stents in years 2 and 3. The adjusted relative risk of the composite outcome of death or repeat revascularization associated with drug-eluting stents relative to bare-metal stents was 0.73 early in the first year of follow-up; it then rose gradually over time, to a peak of 2.24 at 3 years.

Interpretation: Drug-eluting stents are safe and effective in the first year following insertion. Thereafter, the possibility of longer term adverse events cannot be ruled out.

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Drug-eluting stents now comprise at least 85% of stents used in the United States and up to 40% or more of stents elsewhere. The overwhelming worldwide use of drug-eluting stents has, however, been tempered by the cost differential to bare-metal stents, the lack of data on long-term outcomes in large patient populations and, more recently, emerging concerns about safety because of reports of late thrombosis.[1–8]

The use of stents has been shown to reduce the rates of repeat revascularization and restenosis after angioplasty compared with angioplasty alone.[9] Despite this, the long-term efficacy of stent use has been limited by the need for repeat revascularization owing to restenosis.[10] Drug-eluting stents were developed to address this problem. Both clinical trials[11–20] and registry data[21–25] have shown reduced rates of restenosis with drug-eluting stents up to 4 years after implantation. This advantage appears to extend to patients with acute coronary syndromes: a recent 2-year follow-up study involving 7217 patients with acute coronary syndromes suggested that rates of death were lower among patients with drug-eluting stents than among those with bare-metal stents.[26]

The possibility of late thrombosis associated with drug-eluting stents is, however, a concern. Rates of late thrombosis have been reported to be 3.6–5.9 events per 1000 patients receiving drug-eluting stents.[27] This adverse event has been the subject of a review by the US Food and Drug Administration and has captured the attention of authoritative bodies around the world.

Because of concerns about the long-term safety of drug-eluting stents, we compared the rates of death and of death or repeat revascularization over 3 years among patients who received either bare-metal or drug-eluting stents during angioplasty.

Methods

Study design and patient population

We assembled a prospective cohort of all patients undergoing percutaneous coronary intervention with either bare-metal or

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drug-eluting stents between Apr. 1, 2003, and Mar. 31, 2006. Patients were followed up to Mar. 31, 2007. We chose the date of Apr. 1, 2003, to coincide with the date that drug-eluting stents were approved for use in Canada.

The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) is an initiative for a prospective, geographically defined clinical registry that captures detailed clinical information on all patients undergoing catheterization in the province of Alberta (population about 3 million). Data collection for the registry began in 1995, with patients followed longitudinally for assessment of clinical, health-related quality-of-life and economic outcomes.[28] Validation and enhancement of data are performed with the use of a validated methodology.[29,30]

For our study, we recorded the following clinical variables at the time of catheterization: patient age and sex, presence of congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, renal disease (as indicated by elevated serum creatinine level), diabetes mellitus, dialysis status, hyperlipidemia, hypertension, liver or gastrointestinal disease, malignant disease, smoking status (categorized as "never," "former" or "current"), prior myocardial infarction (anytime), prior coronary artery bypass graft surgery, prior percutaneous coronary intervention and use of glycoprotein IIb/IIIa inhibitors. In addition, we recorded the primary indication for catheterization as acute coronary syndrome (myocardial infarction within 8 weeks before catheterization or unstable angina), non-acute coronary syndrome (stable angina) or "other."

We recorded the extent of coronary disease and derived the weighted Duke Index and Duke Myocardial Jeopardy score, an estimate of the percentage of myocardium at risk given the extent of coronary disease.[31] We graded left ventricular ejection fraction into 5 categories: less than 20%, 20%–34%, 35%–50%, more than 50% and "ventriculogram not done." We recorded details of the percutaneous coronary intervention, including use of stent, type of stent (drug-eluting or bare metal), length of stent and number of stents.

Outcomes

We determined the occurrence of death through a semiannual linkage to data from the Alberta Bureau of Vital Statistics. We obtained information on subsequent revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery) from the APPROACH database. For the purposes of this paper, we chose all-cause mortality and a composite outcome of death or repeat revascularization as the outcomes of interest.

Statistical analysis

We used the χ^2 test to compare the clinical and demographic characteristics of patients who received drug-eluting stents with those of patients who received bare-metal stents. We analyzed outcomes at 1 year because we had follow-up data for all patients to at least 1 year. We used logistic regression analysis to calculate risk-adjusted odds ratios (ORs) for death and the composite outcome of death or repeat revascularization at 30 days and at 1 year. ORs below 1.0 indicate a decreased risk of events among patients who received drug-eluting stents.

For survival beyond 1 year, we used Kaplan–Meier survival analyses to compare crude survival and rates of the composite outcome of death or repeat revascularization over the 3-year follow-up period. The survival analyses accounted for censoring of patients when follow-up ended without an event. Next, we extended our survival analysis to include a spline analysis — an analytical technique that dynamically determines the relative risk at moments in time — both in unadjusted and risk-adjusted forms for the 3 years of follow-up. Comprehensive risk adjustment was conducted to account for all of the baseline clinical risk variables presented in Table 1. Spline analysis is a graphical technique that plots the relative risk associated with drug-eluting stents relative to bare-metal stents against time using Schoenfeld residuals.[32,33] The resulting curves show the change in relative risk over time, with 95% confidence intervals.

For a sensitivity analysis, we used propensity scores to compare the outcomes of patients in the 2 stent groups. The likelihood (or propensity) to receive drug-eluting stents was modelled, and we then compared outcomes of the 2 groups across tertiles of likelihood to receive drug-eluting stents. We extended the propensity analysis to conduct a 1-to-1 match of each patient with drug-eluting stents to a single patient with bare-metal stents, matched by their propensity to receive drug-eluting stents.

Results

A total of 6471 patients underwent percutaneous coronary intervention with stenting. Of these patients, 1120 (17.3%) received drug-eluting stents, and 5320 (82.2%) received bare-metal stents. Another 31 patients had undeployed stents and were excluded from further analysis. Patients with drug-eluting stents were more likely than those with bare-metal stents to be female and to have a higher rate of renal disease, diabetes mellitus, hyperlipidemia and hypertension (Table 1).

Complete follow-up data for all patients to at least the end of year 1 allowed us to estimate all event rates precisely at 30 days, 6 months and 1 year (Table 2). The 30-day mortality was significantly lower among patients who received drug-eluting stents than among those with bare-metal stents (0.7% v. 1.8%, risk-adjusted odds ratio [OR] 0.50, 95% confidence interval [CI] 0.33–0.76). This difference persisted to the end of year 1 (3.0% v. 3.7%, risk-adjusted OR 0.62, 95% CI 0.46–0.83). The rate of the composite outcome of death or repeat revascularization was significantly lower in the drug-eluting stent group than in the bare-metal stent group at 30 days and at the end of year 1 (4.1% v. 6.3%, adjusted OR 0.42, 95% CI 0.31–0.57 at 30 days; 12.0% v. 15.8%, adjusted OR 0.40, 95% CI 0.33–0.49 at 1 year). We noted the same general findings among patients with acute coronary syndromes. Among patients with non-acute coronary syndromes (i.e., stable angina), we did not detect statistically significant differences in either mortality or the composite outcome at any point between the 2 stent groups.

Table 1: Characteristics of patients who underwent coronary angioplasty, by type of stent received

Characteristic	Type of stent; no. (%) of patients*		
	Bare metal *n = 5320*	Drug-eluting *n = 1120*	*p* value
Age, yr, mean (SD)	62.5 (11.9)	62.3 (11.6)	0.6
Sex, male	4022 (75.6)	799 (71.3)	0.002
Congestive heart failure	527 (9.9)	91 (8.1)	0.06
Peripheral vascular disease	319 (6.0)	69 (6.2)	0.81
Cerebrovascular disease	298 (5.6)	76 (6.8)	0.14
Chronic pulmonary disease	761 (14.3)	147 (13.1)	0.31
Renal disease†	266 (5.0)	83 (7.4)	0.001
Diabetes mellitus	1106 (20.8)	367 (32.8)	< 0.001
Dialysis	48 (0.9)	19 (1.7)	0.02
Hyperlipidemia	4298 (80.8)	983 (87.8)	< 0.001
Hypertension	3532 (66.4)	791 (70.6)	0.006
Liver or gastrointestinal disease	404 (7.6)	99 (8.8)	0.19
Malignant disease	207 (3.9)	41 (3.7)	0.72
Current smoker	1899 (35.7)	277 (24.7)	< 0.001
Former smoker	1665 (31.3)	416 (37.1)	< 0.001
Prior myocardial infarction	3059 (57.5)	510 (45.5)	< 0.001
Prior coronary artery byass graft surgery	303 (5.7)	132 (11.8)	< 0.001
Prior percutaneous coronary intervention	197 (3.7)	60 (5.4)	0.01
Use of glycoprotein IIb/IIIa inhibitors	2777 (52.2)	627 (56.0)	0.02
Primary indication for angioplasty			
Acute coronary syndrome	4460 (83.8)	726 (64.8)	< 0.001
Non-acute coronary syndrome	848 (15.9)	387 (34.6)	< 0.001
Other	12 (0.2)	7 (0.6)	< 0.001
Length of stent, mm, mean (SD)	16.6 (6.1)	17.7 (7.7)	< 0.001
Diameter of stent, mm, mean (SD)	3.6 (1.4)	3.3 (1.3)	< 0.001
Duke Myocardial Jeopardy score,‡ mean (SD)	42.4 (22.6)	50.5 (23.1)	< 0.001
Ejection fraction			
> 50	3155 (59.3)	665 (59.4)	0.03
35–50	1239 (23.3)	219 (19.6)	0.03
20–34	197 (3.7)	47 (4.2)	0.03
< 20	37 (0.7)	9 (0.8)	0.03
Ventriculogram not done	692 (13.0)	180 (16.1)	
Anatomy§			
Low risk	3400 (63.9)	604 (53.9)	0.01
High risk	1617 (30.4)	431 (38.5)	0.01
Left main	117 (2.2)	57 (5.1)	0.01
Data missing	186 (3.5)	28 (2.5)	
No. of stents, mean (SD)	1.75 (1.02)	1.46 (0.77)	< 0.001
No. of stents			< 0.001
1	2793 (52.5)	750 (67.0)	
2	1612 (30.3)	263 (23.5)	
3	557 (10.5)	80 (7.1)	
4	248 (4.7)	19 (1.7)	
≥ 5	110 (2.1)	8 (0.7)	

*Unless stated otherwise.
†As indicated by elevated serum creatinine level.
‡An estimate of the percentage of myocardium at risk given the extent of coronary artery disease.
§High risk includes 3-vessel disease, or 2-vessel disease with disease of the proximal left anterior descending artery; low risk includes other 2-vessel disease, 1-vessel disease, lesions with < 50% stenosis and normal anatomy.

Figure 1 presents the Kaplan–Meier survival curves over the 3 years of follow-up. The survival curves for patients with acute coronary syndromes and for those with non-acute coronary syndromes were similar to the survival curves for the overall study population. When we examined overall event-free survival for the combined outcome (i.e., no death or repeat revascularization), we observed a similar pattern (Figure 2). There were only small differences in survival at year 3 (79.4% v. 78.5%, p = 0.15). The subgroup of patients with acute coronary syndromes had the same general pattern of survival (Figure 2, middle panel). In the subgroup with non-acute coronary syndromes, the differences in event-free survival between the 2 stent groups over time were not significant (Figure 2, bottom panel).

Our stratified analysis of propensity scores revealed that the 1-year mortality was better among patients with drug-eluting stents than among those with bare-metal stents in the 2 tertiles of higher propensity to receive drug-eluting stents (Appendix 1, available at www.cmaj.ca/cgi/content/full/180/2/167/DC2). In the extended propensity analysis in which we conducted a 1-to-1 match of each patient with drug-eluting stents to a single patient with bare-metal stents, we found that survival was again better for patients with drug-eluting stents than for those with bare-metal stents (2.7% v. 4.3% for death, p = 0.043; 11.7% v. 12.7% for the combined outcome of death or repeat revascularization, p = 0.46) (Appendix 1).

Time-dependent spline analysis

In our time-dependent spline analysis, we observed an initial survival benefit with drug-eluting stents (Figure 3, top panel). Over time the effect diminished, with the relative risk

Table 2: Outcomes in the first year after stent insertion, by type of stent

Outcome	Type of stent; no. (%) of patients		p value	Odds ratio (95% confidence interval)	
	Bare metal	Drug-eluting		Crude*	Adjusted†
All patients	*n = 5320*	*n = 1120*			
Death					
30 days	96 (1.8)	8 (0.7)	0.008	0.50 (0.33–0.76)	0.40 (0.25–0.64)
6 months	151 (2.8)	21 (1.9)	0.07	0.62 (0.45–0.85)	0.53 (0.37–0.75)
1 year	195 (3.7)	33 (3.0)	0.24	0.74 (0.57–0.96)	0.62 (0.46–0.83)
Composite outcome‡					
30 days	335 (6.3)	46 (4.1)	0.004	0.44 (0.33–0.58)	0.42 (0.31–0.57)
6 months	665 (12.5)	100 (8.9)	0.007	0.44 (0.36–0.53)	0.38 (0.30–0.48)
1 year	841 (15.8)	134 (12.0)	0.001	0.47 (0.40–0.56)	0.40 (0.33–0.49)
Patients with acute coronary syndromes	*n = 4195*	*n = 669*			
Death					
30 days	84 (2.0)	6 (0.9)	0.05	0.60 (0.35–1.03)	0.46 (0.25–0.87)
6 months	130 (3.1)	16 (2.4)	0.33	0.78 (0.53–1.17)	0.59 (0.36–0.94)
1 year	168 (4.0)	24 (3.6)	0.61	0.88 (0.63–1.23)	0.68 (0.46–1.01)
Composite outcome‡					
30 days	298 (7.1)	34 (5.1)	0.05	0.58 (0.41–0.81)	0.55 (0.37–0.80)
6 months	558 (13.3)	62 (9.3)	0.004	0.54 (0.42,0.70)	0.45 (0.33–0.61)
1 year	696 (16.6)	79 (11.8)	0.002	0.56 (0.45–0.70)	0.46 (0.35–0.61)
Patients with non-acute coronary syndromes	*n = 1125*	*n = 451*			
Death					
30 days	12 (1.1)	2 (0.4)	0.23	0.61 (0.30–1.28)	0.49 (0.22–1.11)
6 months	23 (2.0)	5 (1.1)	0.24	0.61 (0.36–1.04)	0.56 (0.31–1.01)
1 year	27 (2.4)	9 (2.0)	0.63	0.82 (0.53–1.27)	0.69 (0.42–1.13)
Composite outcome‡					
30 days	39 (3.5)	12 (2.7)	0.41	0.55 (0.32–0.95)	0.52 (0.29–0.93)
6 months	111 (9.9)	38 (8.4)	0.38	0.47 (0.34–0.66)	0.46 (0.32–0.67)
1 year	146 (13.0)	55 (12.2)	0.67	0.53 (0.40–0.71)	0.49 (0.35–0.67)

*Baseline group is drug-eluting stents.
†Adjusted for age, sex, comorbidities, indication, use of glycoprotein IIb/IIIa inhibitors, mean length and diameter of stent, ejection fraction, coronary anatomy and Duke Myocardial Jeopardy score.
‡Death or repeat revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery).

crossing 1.0 and indicating better survival with the bare-metal stents.

The corresponding analysis for the combined outcome of death or repeat revascularization showed a similar pattern (Figure 3, bottom panel). During the initial period, outcomes were better with the drug-eluting stents than with the bare-metal stents. Over time, the effect shifted, with the relative risk for the combined outcome favouring bare-metal stents from about 240 days onward. The descriptive statements presented here for Figure 3 emphasize the point estimates for the relative risks at individual moments in time, without attention to statistical significance at each moment. The figure does, however, present bands for the 95% confidence intervals to inform judgments of statistical significance over time.

After we adjusted the spline analysis for baseline risk factors, we found that the findings were similar to those of the unadjusted analysis (Figure 4). Again, there was an initial pattern of decreased risk of events with the drug-eluting stents, followed by a gradual transition over time toward better outcomes with the bare-metal stents. The adjusted relative risk of the composite outcome of death or repeat revascularization associated with drug-eluting stents relative to bare-metal stents was 0.73 early in the first year of follow-up; it then rose gradually over time, to a peak of 2.24 at 3 years.

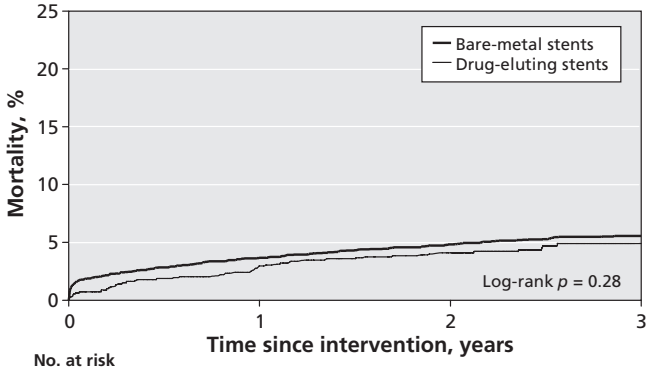
Interpretation

Our study showed that patients who received drug-eluting stents during percutaneous coronary interventions had improved survival and lower rates of repeat revascularization in the first year of follow-up compared with patients who received bare-metal stents. However, our time-dependent spline analysis extending to 3 years showed an increased risk of death and repeat revascularization over time associated with the drug-eluting stents relative to the bare-metal stents.

The early studies of the efficacy of drug-eluting stents focused on outcomes in the shorter term, and in some cases restenosis of target vessels as the primary outcome.[11,12,34] Our findings build on the results of more recent studies, some of which included patients in usual-care settings or had longer follow-up, or both.[5,21,23–26,35]

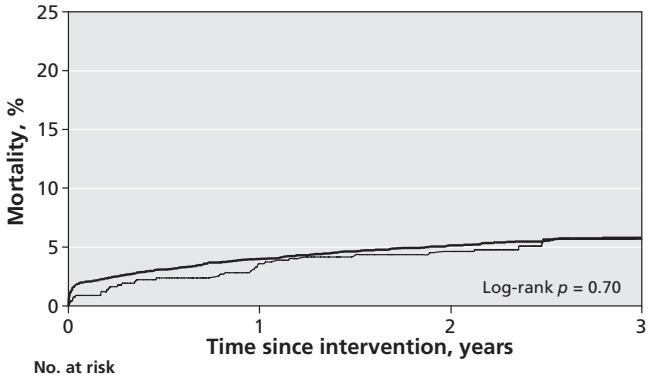
Despite recent concerns about the safety of drug-eluting stents, we did not detect an overwhelming increase in the risk of death among patients who received this type of stent. Also, we did not observe any notable survival drops or clusters of deaths, particularly when the survival of patients with drug-eluting stents was juxtaposed with that of patients with bare-metal stents.

All patients



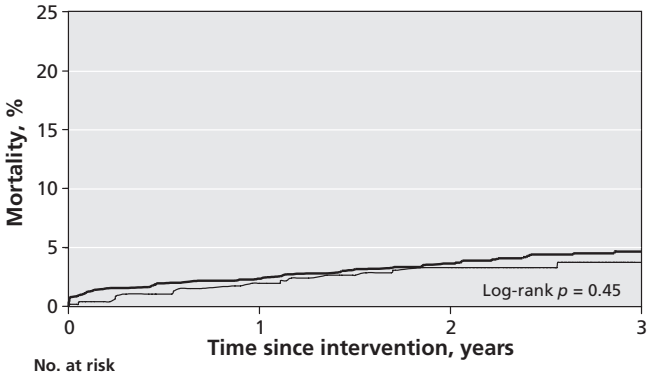
No. at risk			
Bare-metal stents	5125	5064	5031
Drug-eluting stents	1087	1074	1069
No. of events			
Bare-metal stents	195	256	289
Drug-eluting stents	33	46	51

Patients with acute coronary syndromes



No. at risk			
Bare-metal stents	4027	3980	3957
Drug-eluting stents	645	638	634
No. of events			
Bare-metal stents	168	215	238
Drug-eluting stents	24	31	35

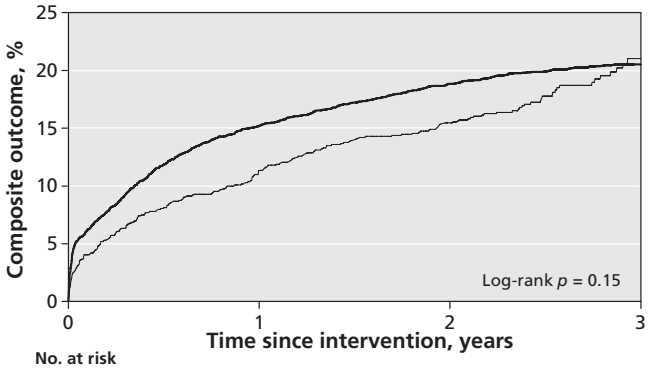
Patients with non-acute coronary syndromes



No. at risk			
Bare-metal stents	1098	1084	1074
Drug-eluting stents	442	436	435
No. of events			
Bare-metal stents	27	41	51
Drug-eluting stents	9	15	16

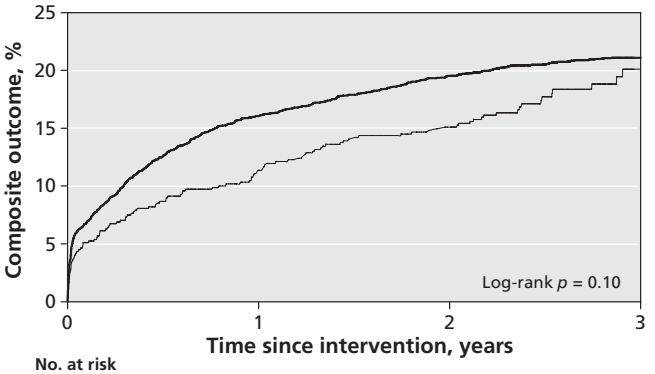
Figure 1: Unadjusted time to death among patients with bare-metal stents and those with drug-eluting stents. Top panel: all patients (n = 6440); middle panel: patients with acute coronary syndromes (n = 4864); bottom panel: patients with non-acute coronary syndromes (n = 1576).

All patients



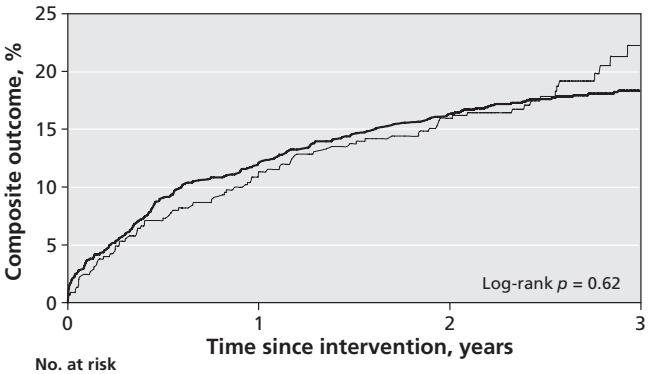
No. at risk			
Bare-metal stents	4511	4317	2199
Drug-eluting stents	993	945	151
No. of events			
Bare-metal stents	809	1003	1078
Drug-eluting stents	127	173	204

Patients with acute coronary syndromes



No. at risk			
Bare-metal stents	3522	3371	1693
Drug-eluting stents	593	567	89
No. of events			
Bare-metal stents	673	819	875
Drug-eluting stents	76	101	119

Patients with non-acute coronary syndromes



No. at risk			
Bare-metal stents	989	941	506
Drug-eluting stents	400	378	62
No. of events			
Bare-metal stents	136	184	203
Drug-eluting stents	51	72	85

Figure 2: Unadjusted time to composite outcome (death or repeat revascularization) among patients with bare-metal stents and those with drug-eluting stents. Top panel: all patients (n = 6440); middle panel: patients with acute coronary syndromes (n = 4864); bottom panel: patients with non-acute coronary syndromes (n = 1576).

Patients who received drug-eluting stents in our study had different baseline characteristics than those who received bare-metal stents. Drug-eluting stents appeared to be used in an appropriate manner, specifically when the risk of restenosis was known to be increased (i.e., in longer lesions, in smaller vessels, and in patients with diabetes). In the early years of our study, there appeared to be a relative aversion to the use of drug-eluting stents in patients with acute coronary syndromes. At the time, this clinical situation lacked the support of data from recently published randomized controlled trials supporting the use of drug-eluting stents in patients with ST-segment elevation myocardial infarction.[36,37]

The focus of our study — the long-term survival of patients with drug-eluting stents — enables inferences on the long-term safety profile of stents in light of the recent concerns about drug-eluting stents. Our comparison of the 2 types of stents was not a randomized controlled trial. Therefore, because of potential selection bias and unmeasured risks, we caution readers not to interpret our study as an efficacy analysis.

Despite these limitations, we did perform a risk-adjusted time-dependent outcome analysis to assess the relative risk of adverse events associated with drug-eluting stents relative to bare-metal stents. Interestingly, our findings suggest that the pace of occurrence of adverse events among patients who received drug-eluting stents was not uniform. In fact, there may have been a slight acceleration of events at about 1 year after the percutaneous coronary intervention, in both the unadjusted and risk-adjusted analyses. The potential pathophysiologic factors underlying this observation are not clear. The typical pattern of stopping thiopyridine therapy between 6 months and 1 year after stent placement may be a contributing factor.[38] Despite the possible acceleration of adverse events at about 1 year, however, the overall survival of patients with drug-eluting stents remained favourable relative to that of patients with bare-metal stents, at least over 3 years of follow-up.

Strengths and limitations

Our study provides new insights into the long-term safety profile of drug-eluting stents. Indeed, data on the long-term follow-up of patients after stent placement are limited outside of clinical trials. Aside from the studies by Lagerqvist and colleagues[23] and Marzocchi and colleagues,[35] the principal reports in this area have described populations with exclusive[11] or near exclusive[22] use of drug-eluting stents with comparison to historical controls. We provide a description of the long-term safety of drug-eluting stents compared with

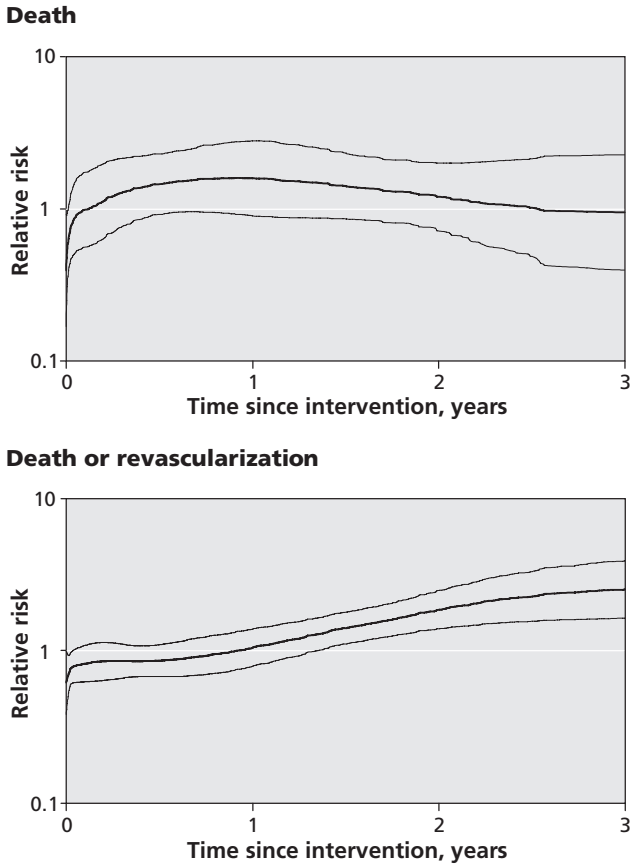


Figure 3: Unadjusted spline analysis of the relative risk of death (top panel) and the composite outcome of death or repeat revascularization (bottom panel) among patients with drug-eluting stents (v. those with bare-metal stents) over the 3-year follow-up period. A relative risk below 1.0 indicates a decreased risk of events among patients with drug-eluting stents. The thin lines above and below the thicker line represent 95% confidence intervals.

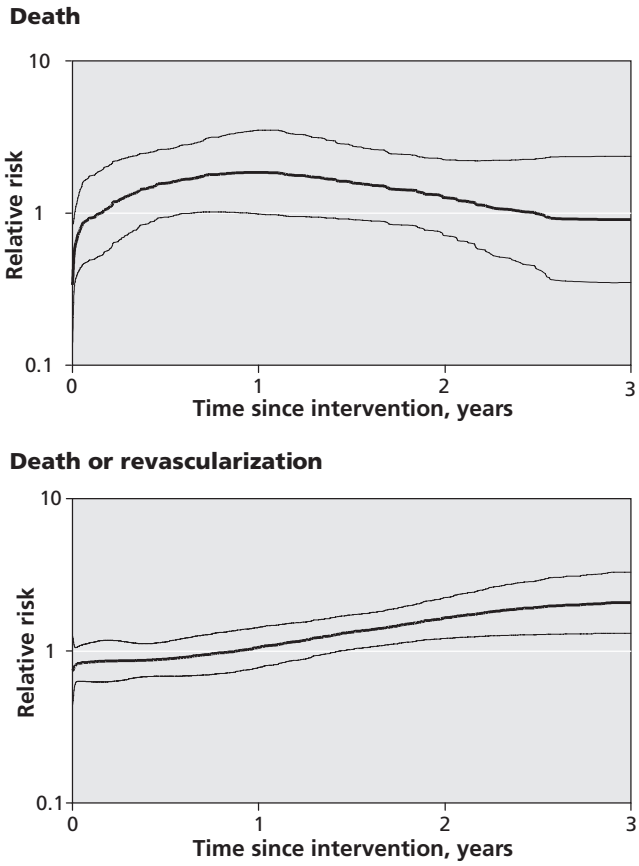


Figure 4: Risk-adjusted spline analysis of the relative risk of death (top panel) and the composite outcome of death or repeat revascularization (bottom panel) among patients with drug-eluting stents (v. those with bare-metal stents) over the 3-year follow-up period. A relative risk below 1.0 indicates a decreased risk of events among patients with drug-eluting stents. The thin lines above and below the thicker line represent 95% confidence intervals.

bare-metal stents. Furthermore, our data showed interesting differences in the outcomes between patients with stable angina and those with acute coronary syndromes.

Our study has limitations. Because of the lack of data on long-term medication use, we can only speculate on the potential role the discontinuation of antiplatelet therapy had on the later onset of adverse outcomes in patients with drug-eluting stents. Furthermore, despite a reasonably large sample, our statistical power was not sufficient to comment on small differences in adverse events between the stent groups in the longer term. Also, we confined our analysis of outcomes to death and clinically driven repeat revascularization. However, many patients who experience myocardial infarction following stent insertion would undergo subsequent repeat catheterization, and some may also die. An additional caveat is that, although we performed a careful risk-adjustment analysis, our findings may relate to unmeasured confounding clinical factors, rather than to the type of stent used.[39] Finally, because our composite outcome included repeat revascularization, we probably captured procedures done because of disease progression rather than restenosis. However, this limitation probably did not significantly affect our analysis of the composite outcome, because disease progression was likely similar in the 2 stent groups.

Conclusions

Our study findings suggest that the long-term survival (to 3 years) of patients with drug-eluting stents remains favourable overall. It is not measurably worse than that of patients with bare-metal stents. Further work, however, is needed to characterize better the possibly dynamic risk profile of drug-eluting stents over time. Also, data are needed on the potential value of long-term dual antiplatelet therapy to protect against late adverse events in patients with drug-eluting stents.

This article has been peer reviewed.

Competing interests: Merril Knudtson received fees from Medtronics for chairing an interventional workshop during the 2006 and 2007 Canadian Cardiovascular Society meetings. None declared for Andrew Philpott, Danielle Southern, Fiona Clement, Diane Galbraith, Mouhieddin Traboulsi or William Ghali.

Contributors: Andrew Philpott developed the study concept and design, compiled background literature and drafted the manuscript. Danielle Southern and Fiona Clement conducted the data analyses. Diane Galbraith oversaw the collection of data from the APPROACH database. Mouhieddin Traboulsi contributed to the study design and literature search. Merril Knudtson is the principal investigator of APPROACH; he contributed to the study design and literature search. William Ghali oversaw and contributed to all aspects of the study, from conception and design, to analysis, to completion of the final manuscript for publication. All of the authors critically revised the manuscript for important intellectual content and approved the final version submitted for publication.

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REFERENCES

1. Feres F, Costa JR Jr, Abizaid A. Very late thrombosis after drug-eluting stents. *Catheter Cardiovasc Interv* 2006;68:83-8.
2. Ishikawa T, Mutoh M, Fuda Y, et al. Documented subacute stent thrombosis within thirty days after stenting with sirolimus-eluting stent (Cypher) for acute myocardial infarction: a Japanese single center retrospective non-randomized study. *Circ J* 2006;70:1091-2.
3. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006;48:193-202.
4. Manjappa N, Agarwal A, Cavusoglu E. Very late bare-metal stent thrombosis. A case report and review of the literature. *J Invasive Cardiol* 2006;18:E203-6.
5. Ong AT, McFadden EP, Regar E, et al. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol* 2005;45:2088-92.
6. Pasceri V, Pelliccia F, Cianfrocca C, et al. Very late thrombosis after sirolimus-eluting stent implantation. *J Cardiovasc Med (Hagerstown)* 2006;7:438-42.
7. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation* 2006;113:2803-9.
8. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: Should we be cautious? *Circulation* 2004;109:701-5.
9. Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents. A hierarchical Bayesian meta-analysis. *Ann Intern Med* 2003;138:777-86.
10. Serruys PW, Kutryk MJB, Ong ATL. Coronary artery stents. *N Engl J Med* 2006; 354:483-95.
11. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773-80.
12. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315-23.
13. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation* 2003;107:38-42.
14. Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 2003;108:788-94.
15. Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomized controlled trial (E-SIRIUS). *Lancet* 2003;362:1093-9.
16. Schampaert E, Cohen EA, Schluter M, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 2004;43:1110-5.
17. Gershlick A, De Scheerder I, Chevalier B, et al. Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European evaLUation of paclitaxel Eluting Stent (ELUTES) trial. *Circulation* 2004;109:487-93.
18. Ardissino D, Cavallini C, Bramucci E, et al. Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. *JAMA* 2004;292:2727-34.
19. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221-31.
20. Kimura T, Yokoi H, Nakagawa Y, et al. Three-year follow-up after implantation of metallic coronary-artery stents. *N Engl J Med* 1996;334:561-6.
21. Williams DO, Abbott JD, Kip KE. Outcomes of 6906 patients undergoing percutaneous coronary intervention in the era of drug-eluting stents: report of the DEScover Registry. *Circulation* 2006;114:2154-62.
22. Jensen LO, Maeng M, Kaltoft A, et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. *J Am Coll Cardiol* 2007;50:463-70.
23. Lagerqvist B, James SK, Stenestrand U, et al. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med* 2007;356:1009-19. Epub 2007 Feb 12.
24. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in Ontario. *N Engl J Med* 2007;357:1393-402.
25. Ong AT, van Domburg RT, Aoki J, et al. Sirolimus-eluting stents remain superior to bare-metal stents at two years: medium-term results from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. *J Am Coll Cardiol* 2006;47:1356-60.
26. Mauri L, Silbaugh TS, Garg P, et al. Drug-eluting or bare-metal stents for acute myocardial infarction. *N Engl J Med* 2008;359:1330-42.
27. Bavry AA, Kumbhani DJ, Helton TJ, et al. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med* 2006;119:1056-61.
28. Ghali WA, Knudtson ML; APPROACH Investigators. Overview of "APPROACH": the Alberta provincial project for outcome assessment in coronary heart disease. *Can J Cardiol* 2000;16:1225-30.
29. Norris CM, Ghali WA, Knudtson ML, et al. Dealing with missing data in observational health care outcome analysis. *J Clin Epidemiol* 2000;53:377-83.
30. Southern DA, Norris CM, Quan H, et al. An administrative data merging solution for dealing with missing data in a clinical registry: adaptation from ICD-9 to ICD-10. *BMC Med Res Methodol* 2008;8:1.
31. Graham MM, Faris PD, Ghali WA, et al.; APPROACH Investigators (Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease). Validation of three myocardial jeopardy scores in a population-based cardiac catheterization cohort. *Am Heart J* 2001;142:254-61.
32. Fleming TR, Harrington DP. *Counting processes and survival analysis.* New York (NY): John Wiley & Sons; 1991.
33. Hastie TJ, Tibshirani RJ. *Generalized additive models*. New York (NY): Chapman & Hall; 1990.
34. Holmes DR Jr, Leon MB, Moses JW, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation* 2004;109:634-40.
35. Marzocchi A, Saia F, Piovaccari G, et al. Long-term safety and efficacy of drug-eluting stents: two-year results of the REAL (REgistro AngiopLastiche dell'Emilia Romagna) multicenter registry. *Circulation* 2007;115:3181-8.
36. Spaulding C, Henry P, Teiger E, et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. *N Engl J Med* 2006;355:1093-104.
37. Laarman GJ, Suttorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N Engl J Med* 2006;355:1105-13.
38. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006;48:2584-91.
39. Daemen J, Serruys PW. Drug-eluting stent update 2007: part II: unsettled issues. *Circulation* 2007;116:961-8.

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