

ORIGINAL ARTICLE

Effectiveness and Safety of Drug-Eluting Stents in Ontario

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ABSTRACT

BACKGROUND

The placement of drug-eluting stents decreases the frequency of repeat revascularization procedures in patients undergoing percutaneous coronary intervention (PCI) in randomized clinical trials. However, there is uncertainty about the effectiveness of drug-eluting stents, and increasing concern about their safety, in routine clinical practice.

METHODS

From the Cardiac Care Network of Ontario's population-based clinical registry of all patients undergoing PCI in Ontario, Canada, we identified a well-balanced cohort of 3751 pairs of patients, matched on the basis of propensity score, who received either bare-metal stents alone or drug-eluting stents alone during an index PCI procedure between December 1, 2003, and March 31, 2005. The primary outcomes of the study were the rates of target-vessel revascularization, myocardial infarction, and death.

RESULTS

The 2-year rate of target-vessel revascularization was significantly lower among patients who received drug-eluting stents than among those who received bare-metal stents (7.4% vs. 10.7%, $P < 0.001$). Drug-eluting stents were associated with significant reductions in the rate of target-vessel revascularization among patients with two or three risk factors for restenosis (i.e., presence of diabetes, small vessels [< 3 mm in diameter], and long lesions [≥ 20 mm]) but not among lower-risk patients. The 3-year mortality rate was significantly higher in the bare-metal-stent group than in the drug-eluting-stent group (7.8% vs. 5.5%, $P < 0.001$), whereas the 2-year rate of myocardial infarction was similar in the two groups (5.2% and 5.7%, respectively; $P = 0.95$).

CONCLUSIONS

Drug-eluting stents are effective in reducing the need for target-vessel revascularization in patients at highest risk for restenosis, without a significantly increased rate of death or myocardial infarction.

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DRUG-ELUTING STENTS HAVE CHANGED the practice of interventional cardiology by significantly reducing the need for repeat revascularization procedures due to restenosis after percutaneous coronary intervention (PCI), as shown in multiple randomized clinical trials.¹⁻⁶ However, there is increasing concern about the safety of drug-eluting stents, in light of reports that they are associated with a slightly increased rate of late stent thrombosis and possibly increased rates of myocardial infarction and death after PCI.^{3,7-9} Although the incidence of stent thrombosis can be reduced with the use of aspirin and clopidogrel therapy, there is uncertainty about how long this therapy is needed, and there are concerns about the costs of prolonged dual antiplatelet therapy and the associated risk of bleeding.¹⁰⁻¹⁴

In this study, we examined a database, initiated in 2003 in Ontario, Canada, in which outcome data from all patients undergoing a PCI and receiving a coronary stent are recorded. We compared the outcomes for the patients who received a drug-eluting stent and those for patients who received a bare-metal stent during the first 16 months of a new provincial program to monitor the introduction and use of drug-eluting stents in Ontario.^{15,16} During this period, Ontario had a policy of providing 1 year of clopidogrel therapy after PCI for patients receiving either type of stent who were 65 years of age or older and who were enrolled in the universal Ontario Drug Benefits plan.

We studied the effectiveness and safety of both types of stents, using a propensity-score–matched cohort of patients who received either a drug-eluting stent alone or a bare-metal stent alone.¹⁷ We also studied the use of three well-established risk factors for restenosis (presence of diabetes, small vessels, and long lesions) to predict which patients have the greatest benefit from implantation of a drug-eluting stent.^{18,19}

METHODS

DATA SOURCES

The Cardiac Care Network (CCN) of Ontario maintains a prospective clinical registry of all patients undergoing invasive cardiac procedures in Ontario that are funded by the government. Clinical nurse research coordinators gather information on each patient from cardiac-procedure referral forms completed by the referring physician and from charts of patients. The registry includes information on

demographic characteristics of patients and their cardiac history, cardiac procedures, and relevant coexisting conditions. All 12 PCI centers in Ontario were required to collect additional data on patients receiving a bare-metal stent or a drug-eluting stent in this registry, as a condition of receiving incremental funding for drug-eluting stents.

For the current study, we used the detailed clinical and stent information captured in the CCN PCI registry and supplemented it by linking that information to other population-based administrative databases in Ontario, using unique encrypted identifiers of patients. We identified an index cohort of all 18,314 patients who underwent a PCI with placement of either a single drug-eluting or bare-metal stent, or multiple stents (all the same type), in Ontario between December 1, 2003, and March 31, 2005. A total of 4961 patients were excluded from this cohort. Patients who had an invalid Ontario health card number were excluded because we could not ascertain their long-term outcomes. Patients who had missing information on potentially important prognostic factors such as socioeconomic status, type or location of lesion, or Canadian Cardiovascular Society angina classification were excluded because of our inability to use their propensity scores for matching. We also excluded from our index cohort any patient who had undergone a previous PCI in the past year. Patients undergoing PCI for left main coronary artery disease were excluded because of concern that there would not be a sufficient number of patients receiving bare-metal stents to allow for propensity-score matching. If a patient who had an index PCI had a second PCI within 1 year after the index (first) PCI, the second PCI was not included in the creation of the index PCI cohort.

We identified the presence or absence of various coexisting conditions using the CCN PCI database and supplemented this information with data from the 24 secondary-diagnosis fields in the hospital-discharge administrative database of the Canadian Institute for Health Information.²⁰ The socioeconomic status of patients was inferred from Statistics Canada census data on the median household income for each geographic area.²¹ Study patients were grouped into five quintiles, according to the income level of their neighborhoods, with similar numbers of patients in the five quintiles.

Clinical outcomes were identified through linkages to clinical and administrative databases, with

the use of the most recent follow-up data that were available; a minimum of 1 year of follow-up data was required for inclusion in the study. Target-vessel revascularization was defined as a follow-up PCI performed in the same vessel as the index PCI, a follow-up PCI without implantation of a stent, or coronary-artery bypass grafting, as recorded in the CCN database through March 31, 2006. We collected data on admissions for myocardial infarction (codes I21 and I22 in the *International Classification of Diseases, 10th Revision*), before and after the index PCI, through March 31, 2006, using linkages to the Canadian Institute for Health Information database.²² Deaths from any cause were identified through November 30, 2006, by means of a linkage to the Ontario Registered Persons Database. The median duration of follow-up for death was similar in the drug-eluting-stent group (840 days) and the bare-metal-stent group (817 days).

Our study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre. The requirement for written informed consent from patients was waived, since participation in the CCN database is mandatory under Ontario's legislation regarding the privacy of health information.

STATISTICAL ANALYSIS

Before performing propensity-score matching, we conducted a univariate analysis of all potentially available explanatory factors for target-vessel revascularization, myocardial infarction, or death. A total of 21 factors were identified that were significantly associated with one or more of these three primary outcomes ($P < 0.05$). We compared the prevalences of these risk factors in the bare-metal-stent group and the drug-eluting-stent group before the propensity-score matching, using a t-test for means and chi-square tests for percentages.

A propensity score for the predicted probability of receipt of a drug-eluting stent in each patient was estimated with the use of a logistic-regression model fit with the 21 factors. We created a propensity-score-matched cohort by attempting to match each patient who received a drug-eluting stent with one who received a bare-metal stent (a 1:1 match). A nearest-neighbor-matching algorithm with a "greedy" heuristic (one that always implements the best immediate, or local, solution) was used to match patients on the basis of their diabetes status (presence or absence of diabetes)

and the logit of their propensity score, with matching occurring if the difference in the logits of the propensity scores was less than 0.2 times the standard deviation of the scores (the caliper width).²³ In greedy nearest-neighbor matching, a patient with a drug-eluting stent was randomly selected and matching was attempted with the "nearest" patient with a bare-metal stent. This process was repeated until matches had been attempted for all patients with drug-eluting stents. Each matched pair was unique, and data for unmatched patients in either group were not used in subsequent analyses.

We also assessed the degree of balance in measured covariates between the drug-eluting-stent group and the bare-metal-stent group. The distributions of categorical variables and continuous variables between the two groups in the matched cohort were compared with the use of McNemar's test and paired t-tests, respectively. We computed the standardized difference between the two groups for each type of distribution, with differences of less than 0.1 taken to indicate good balance in the matched cohort.¹⁷ Kaplan-Meier survival curves were estimated in the matched cohort for patients who received a drug-eluting stent and those who received a bare-metal stent. The survival curves were compared according to methods appropriate for matched data.²⁴

In prespecified subgroup analyses of target-vessel revascularization, patients in the drug-eluting-stent group and those in the bare-metal-stent group were matched on the basis of lesion length (long [≥ 20 mm] vs. short [< 20 mm]), vessel diameter (small [< 3 mm] vs. large [≥ 3 mm]), diabetes status (presence vs. absence of diabetes), and the logit of the propensity score. The total stent length was used as a proxy for lesion length, and the narrowest diameter of the inserted stents was used as a proxy for vessel diameter. Within each of the eight subgroups, the reduction in the risk of the outcome was compared between the drug-eluting-stent group and the bare-metal-stent group with the use of a Cox regression model, with stent type as the sole predictor variable. Robust standard errors that accounted for the clustering of pairs in the matched cohort were obtained. The number of patients who would need to be treated to prevent one target-vessel revascularization with the use of a drug-eluting stent was also calculated for each of the eight subgroups.²⁵

All reported P values are two-sided, and P val-

ues of less than 0.05 were considered to indicate statistical significance. SAS software, version 9.1 (SAS Institute), and the R programming language were used for statistical analyses.

RESULTS

CHARACTERISTICS OF PATIENTS

Before Propensity-Score Matching

A total of 13,353 patients met the study inclusion criteria and met none of the exclusion criteria. The characteristics of patients chosen to receive a drug-eluting stent alone as compared with a bare-metal stent alone, according to Ontario's selective funding policy for drug-eluting stents, are shown in Table 1. Overall, 38% of the stents implanted in patients in Ontario during the study period were drug-eluting stents, with the percentage of patients receiving drug-eluting stents remaining roughly constant (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). Patients chosen by their cardiologists to receive a bare-metal stent were more likely than those chosen to receive a drug-eluting stent to have an admission for acute myocardial infarction on the same day their PCI and stent implantation were performed (i.e., were more likely to require primary PCI or rescue PCI). The mean stent diameter was smaller, and the mean stent length was longer, in the drug-eluting–stent group than in the bare-metal–stent group, showing that cardiologists did selectively implant drug-eluting stents in patients at increased risk for restenosis.

After Propensity-Score Matching

After propensity-score matching was completed, there were 3751 matched pairs of patients (Table 2). There were no significant differences between the drug-eluting–stent group and the bare-metal–stent group in any of the 21 characteristics ($P>0.20$ for all comparisons). The standardized difference between the two groups was less than 0.03 for all variables. In the matched cohort, 82.9% of patients in the drug-eluting–stent group received a paclitaxel stent, and 17.1% received a sirolimus stent.

RATES OF TARGET-VESSEL REVASCULARIZATION

Overall, 10.7% of the patients receiving a bare-metal stent and 7.4% of those receiving a drug-eluting stent required target-vessel revascularization by year 2 of follow-up ($P<0.001$) (Fig. 1A and Table 3). The maximal reduction in the need for repeat revascularization from the use of drug-elut-

ing stents was seen at 6 months. The effectiveness of drug-eluting stents in reducing the need for repeat target-vessel revascularization varied widely, with the four subgroups of patients with two or three risk factors for restenosis (i.e., presence of diabetes, small vessels, and long lesions) showing a significant benefit (Table 4). None of the other four subgroups had significant reductions in the rates of target-vessel revascularization. The number needed to treat to prevent one target-vessel revascularization with the use of drug-eluting stents ranged from 10 to 167 among the eight subgroups.

RATES OF MYOCARDIAL INFARCTION AND DEATH

The rate of myocardial infarction after PCI during the 2-year follow-up period did not differ significantly between the two groups ($P=0.95$) (Fig. 1B and Table 3). However, the rate was 0.4 percentage point lower in the drug-eluting–stent group than in the bare-metal–stent group during the first 6 months of follow-up, whereas the rates of myocardial infarction crossed over at approximately 15.6 months of follow-up; the rate was 0.5 percentage point higher in the drug-eluting–stent group by year 2 of follow-up.

The rate of death after PCI in the matched cohort at year 3 of follow-up was 7.8% among patients receiving a bare-metal stent and 5.5% among those receiving a drug-eluting stent ($P<0.001$) (Table 3), with the survival curves gradually diverging over time in favor of drug-eluting stents (Fig. 1C). The composite outcome of death or myocardial infarction also favored drug-eluting stents (Fig. 1D). To investigate the potential contributions of target-vessel revascularization and myocardial infarction to the absolute differences in the survival rate, we compared the 30-day mortality among patients who had each outcome. The 30-day mortality among patients who underwent target-vessel revascularization was 2.5% in the bare-metal–stent group and 2.4% in the drug-eluting–stent group. In contrast, the 30-day mortality among patients who had a myocardial infarction was 6.9% in both groups.

DISCUSSION

Our study provides information from a large population-based database that could be used to help clinicians determine whether a bare-metal stent or drug-eluting stent is better for a particular patient. We found that drug-eluting stents were most effective in reducing the need for target-vessel revas-

Table 1. Baseline Characteristics of Patients, According to Stent Group, before Propensity-Score Matching.*

Characteristic	Bare-Metal Stent (N=8247)	Drug-Eluting Stent (N=5106)	P Value
Age (yr)	62.6±11.8	61.7±11.5	<0.001
Male sex (%)	74.4	70.0	<0.001
Income quintile (%)†			
1	18.8	18.7	0.89
2	20.3	19.9	
3	20.7	21.2	
4	21.5	21.2	
5	18.6	19.0	
Cardiac condition or procedure (%)			
Hypertension	37.1	36.4	0.45
Myocardial infarction			
Same day as index PCI	13.7	7.4	<0.001
1–7 days before index PCI	22.3	18.3	
8–365 days before index PCI	11.3	12.7	
None within 365 days before index PCI	52.7	61.5	
CCS angina classification‡			
0	7.5	6.4	<0.001
I	4.8	5.6	
II	13.8	15.6	
III	20.6	26.2	
IVA	28.4	25.2	
IVB	11.1	10.8	
IVC	12.1	9.4	
IVD	1.7	0.7	
Congestive heart failure	5.0	5.4	0.28
Previous coronary-artery bypass surgery	7.7	9.5	<0.001
PCI >1 yr before index PCI	4.4	6.1	<0.001
Coexisting condition (%)			
Diabetes	24.5	38.0	<0.001
Peripheral vascular disease	5.7	5.8	0.96
Chronic obstructive pulmonary disease	5.3	4.0	<0.001
Cerebrovascular disease	3.6	5.9	<0.001
Primary cancer	1.1	0.9	0.52
Renal failure requiring dialysis	0.8	1.3	0.005
Index PCI			
Ad hoc PCI (%)	58.7	50.5	<0.001
Stent length (mm)	24.7±15.3	28.7±16.8	<0.001
Stent diameter (mm)	3.1±0.5	2.8±0.4	<0.001
No. of stents per patient	1.5±0.8	1.5±0.8	0.98
No. of vessels stented	1.1±0.4	1.1±0.4	0.17
ACC–AHA lesion type (%)			
A	13.2	6.4	<0.001
B1	29.6	25.9	
B2	36.0	37.8	
C	21.1	29.8	

* Plus–minus values are means ±SD. PCI denotes percutaneous coronary intervention, and ACC–AHA American College of Cardiology–American Heart Association.

† The first income quintile is the lowest quintile.

‡ The Canadian Cardiovascular Society (CCS) angina classifications range from 0 (no symptoms) to IVD (shock).

Table 2. Baseline Characteristics of Patients, According to Stent Group, after Propensity-Score Matching.*

Characteristic	Bare-Metal Stent (N=3751)	Drug-Eluting Stent (N=3751)
Age (yr)	62.3±11.7	62.3±11.5
Male sex (%)	70.7	71.2
Income quintile (%)†		
1	19.1	19.5
2	19.5	20.2
3	21.3	20.3
4	21.2	21.2
5	18.8	18.8
Cardiac condition or procedure (%)		
Hypertension	36.6	36.7
Myocardial infarction		
Same day as index PCI	9.1	9.2
1–7 days before index PCI	19.5	19.8
8–365 days before index PCI	12.7	11.9
None within 365 days before index PCI	58.7	59.2
CCS angina classification‡		
0	7.3	6.6
I	5.5	5.4
II	15.1	15.0
III	23.3	23.7
IVA	27.0	26.6
IVB	11.1	11.2
IVC	9.7	10.6
IVD	1.0	0.9
Congestive heart failure	5.0	5.3
Previous coronary-artery bypass surgery	9.0	8.5
PCI >1 yr before index PCI	5.5	5.2
Coexisting condition (%)		
Diabetes	32.6	32.6
Peripheral vascular disease	6.3	5.6
Chronic obstructive pulmonary disease	4.7	4.6
Cerebrovascular disease	4.9	5.2
Primary cancer	1.1	1.1
Renal failure requiring dialysis	1.2	1.1

cularization in patients at the highest risk for restenosis (i.e., those who had two or three risk factors — presence of diabetes, small vessels, and long lesions). In contrast, we found small reductions, which were not significant, in the rates of target-vessel revascularization among patients at low or intermediate risk for restenosis (e.g., those without diabetes and with large vessels or short

lesions). The relatively low rate of clinically driven target-vessel revascularization in most of the subgroups of patients with bare-metal stents in our study is in contrast to the rate of 15 to 20% or higher, in association with protocol-driven angiography and other factors, reported in clinical trials of drug-eluting stents.^{1,3,4}

Although the benefit of drug-eluting stents in

Table 2. (Continued.)

Characteristic	Bare-Metal Stent (N=3751)	Drug-Eluting Stent (N=3751)
Index PCI		
Ad hoc PCI (%)	53.4	53.7
Stent length (mm)	26.3±16.8	26.6±15.2
Stent diameter (mm)	2.8±0.4	2.8±0.4
No. of stents per patient	1.5±0.8	1.5±0.8
No. of vessels stented	1.1±0.4	1.1±0.4
ACC–AHA lesion type (%)		
A	7.6	8.2
B1	29.1	28.9
B2	38.0	37.5
C	25.2	25.4

* Plus–minus values are means ±SD. The exact version of McNemar's test for binary variables and a matched t-test for continuous variables were performed on these data for the propensity-matched cohort. In all comparisons of characteristics of the patients in each of the two groups, P values were not significant ($P>0.20$ for all comparisons), and the groups were well balanced (standardized differences in the mean, <0.03). PCI denotes percutaneous coronary intervention, and ACC–AHA American College of Cardiology–American Heart Association.

† Income quintile 1 is the lowest quintile.

‡ The Canadian Cardiovascular Society (CCS) angina classifications range from 0 (no symptoms) to IVD (shock).

reducing the need for target-vessel revascularization in the real world has been confirmed in a few other, recent registry reports,^{8,26} there has been great concern expressed recently about whether this benefit is outweighed by the risk of late stent thrombosis.^{27–30} Our results suggest that the risk–benefit equation for overall mortality favors drug-eluting stents, since the overall rate of death at year 3 of follow-up was lower in the drug-eluting–stent group than in the bare-metal–stent group. A mortality benefit of drug-eluting stents has not been found in clinical trials conducted to date, but this could reflect the relatively small numbers of patients, limited long-term follow-up, or a lower risk in the populations in many of these studies.^{1–4}

Some have argued that the risk of restenosis, which may be manifested as angina or myocardial infarction, may outweigh the slightly increased rate of late stent thrombosis found in recent studies.³¹ We report a 30-day mortality of 2.5% among patients who received a bare-metal stent and underwent repeat procedures, showing that the need for target-vessel revascularization is a clinically significant adverse event. However, the increased incidence of repeat procedures among our patients who received a bare-metal stent is insufficient to explain fully the small absolute difference in the

survival rate in favor of drug-eluting stents. Alternatively, our mortality data could reflect unmeasured confounding factors, and we suggest caution in concluding, on the basis of our study alone, that drug-eluting stents save lives.

Because we collected follow-up data from linkages to the administrative databases, it was not possible for us to ascertain the exact rate of late stent thrombosis. However, we found that the rate of myocardial infarction was slightly lower in the drug-eluting–stent group than in the bare-metal–stent group during the first 6 months of follow-up, whereas this benefit was lost during the second year, with a slightly higher rate of myocardial infarction in the drug-eluting–stent group at 2 years. This crossover of rates of myocardial infarction in year 2 has also been reported for patients in the Swedish PCI stent registry and is consistent with findings from other studies that have shown an increased frequency of late thrombotic events, such as nonfatal myocardial infarction, among patients receiving a drug-eluting stent within a few months after clopidogrel therapy was stopped.^{8,12,14} If confirmed in additional studies, these results would suggest that dual antiplatelet therapy with aspirin and clopidogrel may need to be continued beyond the 1-year period currently recommended in American and European guidelines.^{10,32,33}

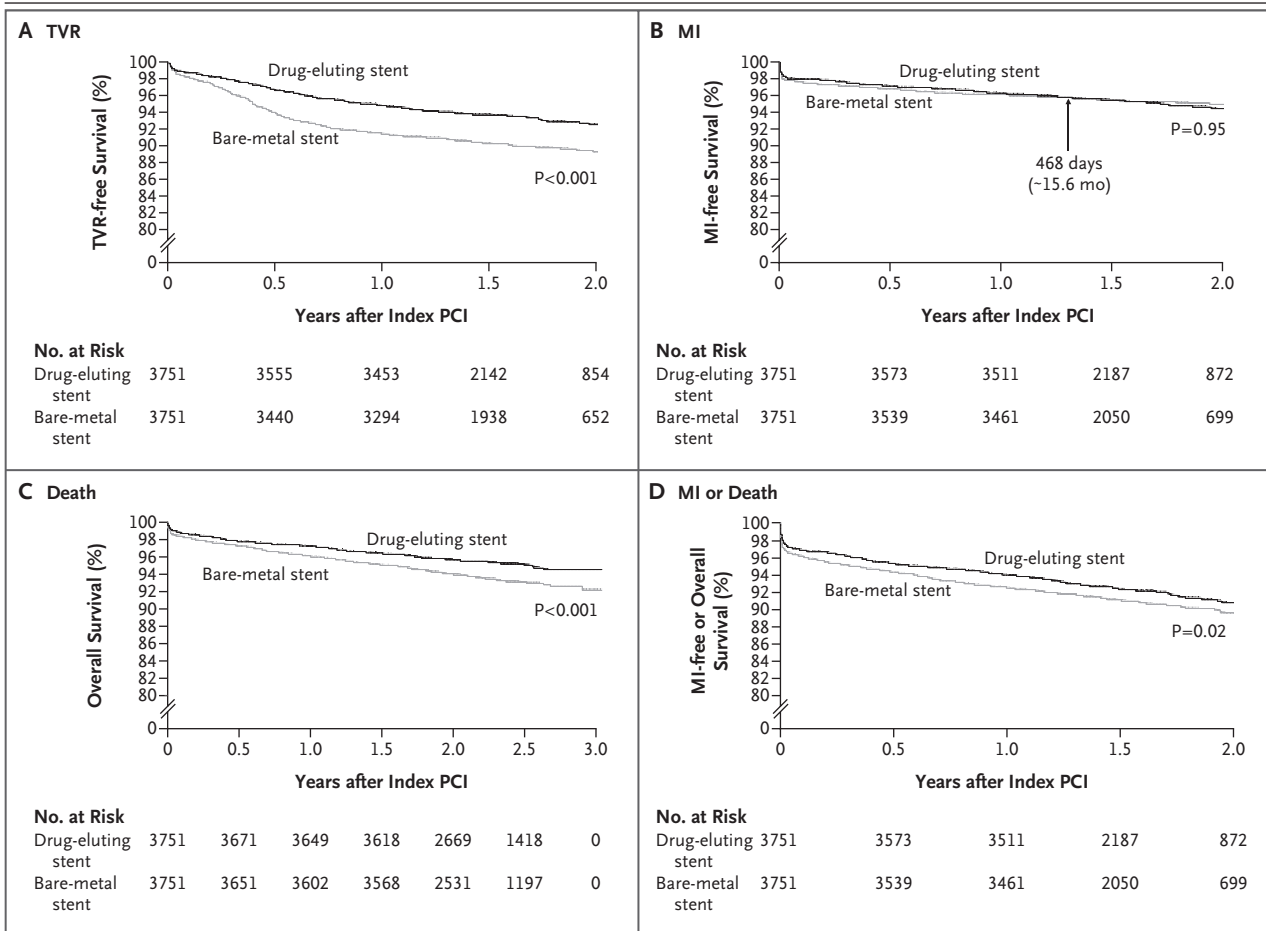


Figure 1. Event-free Survival in a Propensity-Score-Matched Cohort of Patients Who Received a Drug-Eluting Stent or a Bare-Metal Stent. Kaplan–Meier curves are shown for target-vessel revascularization (TVR) (Panel A), myocardial infarction (MI) (Panel B), overall survival (Panel C), and MI-free or overall survival (Panel D) after the index percutaneous coronary intervention (PCI).

Our study has many strengths but also important limitations. The strengths include the availability of a large population-based cohort of patients who underwent PCI, which permitted a comparison of outcomes among patients receiving drug-eluting stents and concurrent controls receiving bare-metal stents with the use of a rigorous cohort analysis involving propensity-score matching. The opportunity to create our data set using multiple linked clinical and administrative databases of Canada’s single-payer universal health care system allowed us to achieve virtually 100% follow-up of outcome rates for both groups of patients. Our study was entirely funded from public sources, without any involvement from industry.

Important limitations of our study include its

observational nature and the fact that our findings may not be generalizable to countries without universal health insurance and drug-benefit plans. The benefits of drug-eluting stents are in part related to the prolonged use of dual antiplatelet therapy, which was available for 1 year at a minimal cost to most patients in our study. Although we were able to establish a large and well-balanced cohort of patients receiving bare-metal stents and patients receiving drug-eluting stents, matched on the basis of the propensity score, our study was not a randomized clinical trial, and there may still be unmeasured confounding factors that contribute to our findings. We did not have access to certain data (e.g., subtypes of myocardial infarction) that would have been of interest.

Table 3. Outcome Rates after Index PCI in the Propensity-Score–Matched Cohort, According to Subgroup.*

Outcome	At 6 Mo		At 1 Yr		At 2 Yr		At 3 Yr		P Value†
	Bare-Metal Stent	Drug-Eluting Stent	Bare-Metal Stent	Drug-Eluting Stent	Bare-Metal Stent	Drug-Eluting Stent	Bare-Metal Stent	Drug-Eluting Stent	
	<i>percent</i>								
Target-vessel revascularization	6.0	3.2	8.6	5.2	10.7	7.4			<0.001
Myocardial infarction	3.3	2.9	3.9	3.8	5.2	5.7			0.95
Death	2.7	2.1	4.0	2.7	6.1	4.3	7.8	5.5	<0.001
Myocardial infarction or death	5.7	4.8	7.5	6.1	10.5	9.3			0.02

* Outcome rates were derived from paired Kaplan–Meier curves. PCI denotes percutaneous coronary intervention.

† P values are for the comparisons of the paired Kaplan–Meier curves.

Table 4. Rates of Target-Vessel Revascularization in the Propensity-Score–Matched Cohort, According to Subgroup.*

Diabetes	Vessel Diameter	Lesion Length	No. of Matched Pairs	Target-Vessel Revascularization		Hazard Ratio (95% CI)†	P Value	No. Needed to Treat
				Bare-Metal Stent	Drug-Eluting Stent			
	<i>percent</i>							
Yes	Small	Long	347	17.6	7.2	0.38 (0.24–0.60)	<0.001	10
Yes	Small	Short	253	13.0	4.7	0.34 (0.17–0.66)	0.002	12
Yes	Large	Long	295	10.5	6.1	0.55 (0.32–0.95)	0.03	23
Yes	Large	Short	291	7.6	6.2	0.78 (0.42–1.43)	0.42	71
No	Small	Long	782	12.3	8.6	0.66 (0.48–0.91)	0.01	27
No	Small	Short	502	8.0	6.8	0.82 (0.51–1.30)	0.40	83
No	Large	Long	638	7.5	5.6	0.74 (0.48–1.15)	0.18	53
No	Large	Short	505	5.9	5.3	0.87 (0.52–1.47)	0.61	167

* Patients were matched on the basis of the logit of the propensity score; diabetes status (presence vs. absence of diabetes); vessel diameter (small [<3 mm] vs. large [≥ 3 mm]); lesion length (short [<20 mm] vs. long [≥ 20 mm]); and other, higher-order terms to improve the balance between the two stent groups.

† Hazard ratios are for the drug-eluting–stent group, as compared with the bare-metal–stent group.

In conclusion, the experience in Ontario, Canada, is that drug-eluting stents are more effective than bare-metal stents in reducing the need for target-vessel revascularization in patients at highest risk for restenosis after PCI but offer minimal benefit to patients at lower risk. The small absolute difference in mortality in favor of drug-eluting stents in our study warrants further investigation and should be confirmed or refuted through large, randomized clinical trials with long-term follow-up.

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REFERENCES

1. Babapulle MN, Joseph L, Bélisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet* 2004;364:583-91.
2. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;356:989-97.
3. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;356:998-1008.
4. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;356:1030-9.
5. 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.
6. Laarman GJ, Suttrop MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N Engl J Med* 2006;355:1105-13.
7. Camenzind E, Steg PG, Wijns W. A meta-analysis of first generation drug eluting stent programs. *Circulation* 2007;115:1440-5.
8. Lagerqvist B, James SK, Stenestrand U, Lindbäck J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med* 2007;356:1009-19.
9. Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med* 2006;119:1056-61.
10. Grines CL, Bonow RO, Casey DE Jr, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation* 2007;115:813-8.
11. 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.
12. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007;297:159-68.
13. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293:2126-30.
14. 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.
15. Working Group on Drug Eluting Stents. Report on initial utilization strategy: final report and recommendations. Toronto: Cardiac Care Network of Ontario, December 2002:15. (Accessed September 7, 2007, at http://www.ccn.on.ca/pdfs%5CFinalDrugElutingMaster2_Dec2002.pdf.)
16. Bowen J, Hopkins R, He Y, et al. Systematic review and cost-effectiveness analysis of drug eluting stents compared to bare metal stents for percutaneous coronary interventions in Ontario: interim report. Report no. HTA002-0512, prepared for the Ontario Ministry of Health and Long-term Care. Hamilton, ON, Canada: Program for Assessment of Technology in Health, McMaster University, December 2005:170. (Accessed September 7, 2007, at <http://www.path-hta.ca/DESreport.pdf>.)
17. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. *Stat Med* 2007;26:734-53.
18. Greenberg D, Bakhai A, Cohen DJ. Can we afford to eliminate restenosis? Can we afford not to? *J Am Coll Cardiol* 2004;43:513-8.
19. Cutlip DE, Chauhan MS, Baim DS, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. *J Am Coll Cardiol* 2002;40:2082-9.
20. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130-9.
21. Wilkins R. Use of postal codes and addresses in the analysis of health data. *Health Rep* 1993;5:157-77.
22. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. *Am Heart J* 2002;144:290-6.
23. Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Stat Med* 2006;25:2084-106.
24. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. New York: Springer-Verlag, 1997.
25. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988;318:1728-33.
26. 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.
27. Shuchman M. Debating the risks of drug-eluting stents. *N Engl J Med* 2007;356:325-8.
28. *Idem*. Trading restenosis for thrombosis? New questions about drug-eluting stents. *N Engl J Med* 2006;355:1949-52.
29. Maisel WH. Unanswered questions — drug-eluting stents and the risk of late thrombosis. *N Engl J Med* 2007;356:981-4.
30. Farb A, Boam AB. Stent thrombosis redux — the FDA perspective. *N Engl J Med* 2007;356:984-7.
31. Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL. Bare metal stent restenosis is not a benign clinical entity. *Am Heart J* 2006;151:1260-4.
32. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 2006;113:e166-e286.
33. Silber S, Albertsson P, Avilés FF, et al. Guidelines for percutaneous coronary interventions. *Eur Heart J* 2005;26:804-47.

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