Published in final edited form as:
Catheter Cardiovasc Interv. 2010 August 1; 76(2): 257–262. doi:10.1002/ccd.22509.

Drug-Eluting Stents versus Bare-Metal Stents for Treatment of Bare-Metal In-Stent Restenosis

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Abstract

Objectives—We compared the long-term outcomes of drug-eluting stents (DES) versus bare-metal stents (BMS) for treatment of bare-metal in-stent restenosis (ISR).

Background—There are no randomized trials or observational studies directly comparing the safety and efficacy of DES versus BMS for treatment of bare-metal ISR.

Methods—We examined data on all patients who underwent percutaneous coronary intervention (PCI) for ISR at Cleveland Clinic between 05/1999 and 06/2007. We compared the efficacy and safety of DES to BMS for treating bare-metal ISR. The primary end point was a composite of death, myocardial infarction (MI), or target lesion revascularization (TLR). The secondary endpoints were individual components of the primary endpoint.

Results—Of the 931 patients identified over 8 years, 706 had bare-metal ISR and met our study criteria. Of the 706 patients with bare-metal ISR, 362 were treated with DES and 344 with BMS. There were 230 cumulative events for a median follow-up of 3.2 years. After adjusting for 27 variables, DES were associated with lower primary endpoint compared to BMS for treatment of bare-metal ISR (21% versus 45%, adjusted hazard ratio [HR] 0.63; 95% confidence interval [CI], 0.42-0.95; p = 0.03). The individual secondary endpoint of death (8% versus 24%, p = 0.005) favored DES, but MI (3% versus 8%, p = 0.31), and TLR (13% versus 20%, p = 0.23) failed to reach statistical significance.

Conclusions—In our multivariate analysis of patients with bare-metal ISR, DES use was associated with significantly lower death, MI, or TLR when compared to BMS.

Keywords

in-stent restenosis; drug-eluting stents; bare-metal stents; vascular brachytherapy; revascularization

Introduction

In-stent restenosis (ISR) continues to be one of the most common adverse events after stenting, affecting 15-35% of lesions treated with bare-metal stents (BMS) (1-5). Bare-metal ISR is not a benign entity and has been associated with both poor survival and acute coronary syndromes (6-8). Currently, local vascular brachytherapy in conjunction with

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Disclosures: Drs. Singh, Filby, Gorodeski, Lincoff and Mr. El Sakr, have no conflicts of interest or disclosures to report.

balloon angioplasty is the only U.S. Food and Drug Administration approved strategy to treat ISR (1,9-11). However, its use has been limited due to logistical and financial challenges, concerns of radiation exposure, evidence of edge restenosis, late "catch-up" restenosis phenomenon, and its association with late thrombosis (1,12,13). Other modalities such as atherectomy, cutting balloon angioplasty, and laser have not shown incremental advantage over balloon angioplasty for ISR (14-16). Treatment of bare-metal ISR with BMS improved both short- and long-term restenosis rates in vessels ≥3 mm when compared to balloon angioplasty alone (17,18). However, this strategy remains associated with a significant restenosis rate of 20% at 1 year and 25% at 4 years (17,18).

Drug eluting stents (DES) reduce the rate of restenosis by over 70% compared to BMS in native coronary lesions (19,20). Therefore, currently DES placement is believed to be the preferred percutaneous strategy for treating bare-metal ISR (1,21-24). However, to date no randomized controlled trials (RCT) have compared DES versus BMS for treating bare-metal ISR. Additionally, there are no observational studies that directly compare DES to BMS for treating bare-metal ISR.

Methods

Study population

We conducted a retrospective analysis on prospectively collected data from the percutaneous coronary intervention (PCI) registry at Cleveland Clinic, in patients who underwent PCI for ISR between 05/1999 through 06/2007. Baseline characteristics, angiographic data, and medications are collected at the time of PCI by trained research coordinators as part of this ongoing registry. The institutional review board waived requirements for informed consent for this institutional PCI registry.

Angiographic characteristics

We defined in-stent restenosis as any within stent or stent edge restenosis as previously established by Mehran and colleagues (25). Procedural and pharamacotherapy characteristics are captured prospectively. Similarly, information regarding balloon pre-dilation, stent size, stent length, maximum balloon dilatation for stent deployment, number of stents per case, residual stenosis, and other important angiographic features were also captured prospectively. Once DES were commercially available in 2003, the choice of stent type (DES versus BMS) was at the discretion of the operator performing the procedure.

Clinical End-points

The primary end point was a composite of all-cause mortality, myocardial infarction (MI), and target lesion revascularization (TLR). The secondary endpoints were individual components of the primary endpoint. Myocardial infarction was defined as occurrence of troponin elevation with electrocardiographic changes or angina. Peri-procedural MI was defined as peri-procedural rise in creatine kinase-MB ≥ 3 times the upper limit of normal (8.8 ng/ml) or MI requiring hospitalization. Patients were prospectively followed through review of hospital records and the Social Security Death Index. In general, data regarding revascularization, MI, and death are obtained prospectively. However, for the purposes of this analysis retrospective chart review was also performed in order to confirm all endpoints and to determine whether revascularization was target vessel or target lesion.

Statistical analysis

Baseline and angiographic characteristics of patients were compared using the Wilcoxon Rank sum test for continuous variables and the chi-square test for categorical variables. Unadjusted differences in outcome were tested using Kaplan-Meier curves. Subsequently,

multivariable adjusted Cox proportional hazards analyses that accounted for baseline demographic features, angiographic variables, treatment assignment and other confounders (Table 1) were performed. In order to account for advances in PCI over time all multivariable models were adjusted for the procedural date. In total we adjusted for over 23 variables. A p-value of 0.05 was used as a cut-off for statistical significance. Analyses were performed with SAS, version 9.1 (SAS Institute, Cary, North Carolina).

Selected sub-groups that have been previously reported to gain the most benefit from DES, including diabetes, vessel size, and lesion length, were chosen for additional analysis (26,27).

Results

Baseline characteristics

A total of 706 patients with bare-metal ISR met our study criteria during the 8 year study period. Of these 362 were treated with DES and 344 were treated with BMS. Baseline and target lesion characteristics, according to stent type, are presented in Table 1. In general, patient and procedural characteristics were similar between both groups. However, patients who received DES were more likely to be male, have diabetes, have a worse New York Heart Association class, have greater use of angiotensin-converting enzyme inhibitors or statin therapy, have more complex lesions or chronic total occlusions, and have greater total stent length (Table 1). Patients who were treated with BMS were more likely to present with unstable angina or multi-vessel disease and have greater use of heparin and glycoprotein IIb/IIIa inhibitors (Table 1). For the 2 groups (DES or BMS) the mean balloon pressure was 14mm Hg. Additionally, the rate of post dilatation using a non-compliant balloon in the DES group was 58% and in the BMS group was 55% with a p-value of 0.34.

Clinical outcomes

DES versus BMS for treating bare-metal ISR—Among 706 patients treated for bare-metal ISR, 230 cumulative events (death, MI or TLR) occurred during a median follow-up of 3.2 years (IQR: 1.6-4.9 years) (Figure 1). Treatment of bare-metal ISR with DES was associated with a lower composite endpoint compared with those who were treated with BMS (adjusted HR, 0.63; 95% CI, 0.42-0.95; p = 0.03) (Table 2). Analysis of secondary endpoints revealed that all-cause mortality was lower with DES than BMS (8% versus 24%, adjusted HR, 0.37; 95 percent CI, 0.18-0.74; p = 0.005) (Table 2). Similarly the rates of MI (3% versus 8%, adjusted HR 0.54; 95% CI, 0.16-1.78; p = 0.31) and TLR (13% versus 20%, adjusted HR 0.67; 95% CI, 0.35-1.29; p = 0.23) trended towards favoring DES, but failed to reach statistical significance (Table 2).

Sub-group analysis—When we limited our analysis to the post-2003 era (after DES became commercially available), DES treatment still remained associated with a lower primary endpoint compared to BMS for bare-metal ISR (Table 3). Patients without diabetes and those with vessel size less than 3.5 mm had better outcomes with DES compared to BMS (Table 3). However, DES use did not demonstrate benefit in patients with diabetes or vessels greater than 3.5 mm (Table 3). Lesion length also did not influence outcomes based on type of stent used (Table 3).

Discussion

Numerous trials have evaluated the safety and efficacy of DES, however there are no published RCT or observational studies directly comparing DES to BMS for treating bare-metal ISR. In our single center cohort of 931 consecutive patients who presented with ISR,

over a period of 8 years, we methodically addressed this issue by a conducting multivariable analysis.

We examined the long term outcomes of patients who were treated with DES or BMS for bare-metal ISR. Our analysis demonstrates that that for treatment of bare-metal ISR, DES use was associated with a lower composite endpoint of all-cause mortality, MI, or TLR, when compared to BMS at over 3 years of follow-up. To our knowledge, this is the first and largest study to directly compare the safety and efficacy of DES versus BMS in patients undergoing PCI for bare-metal ISR. Our results also indicated a decrease in mortality with DES. While we used multiple adjustments the possibility of selection bias and confounding cannot be excluded. Importantly, however, DES was not associated with increased MI rate and led to a lower incidence of revascularization.

In the only RCT comparing BMS to balloon angioplasty for treatment of ISR, both the restenosis rate (27% vs. 49%, $p = 0.007$) and event-free survival (84% vs. 62%, $p = 0.002$) were better after BMS, in patients with vessels ≥3 mm (17). But this benefit was lost in the broader study population (17). Similarly, in an earlier observational study, Mehran and colleagues, showed that BMS did not reduce TLR or death at 1 year compared to balloon angioplasty even though the in-hospital death, Q-wave MI, or TLR were higher with balloon angioplasty than with BMS (5.6% versus 0.7%, $p = 0.02$) (28). More recently Alfonso and colleagues compared sirolimus-eluting stent (SES) to BMS in ISR by using the individual stent arms of 2 separate RCT (BMS versus balloon angioplasty and SES versus balloon angioplasty) (29). In this analysis, both angiographic late loss (0.13 vs. 1.04 mm, $p < 0.001$) and repeat revascularization at 1 year (10.5 vs. 19.6%, $p < 0.05$) favored SES over BMS (29). This advantage of SES over BMS was preserved even in large vessel ISR, an area where BMS has shown a signal for benefit compared to balloon angioplasty alone (17,29). This is in contrast to our sub-group analysis in which smaller vessels (<3.5 mm) benefit from DES but this advantage was lost in larger vessels (≥ 3.5 mm).

Mechanistic and intra-vascular ultrasound studies have shown that the poor performance of BMS treated bare-metal ISR lesions most likely stems from the enhanced stimulation of neointimal hyperplasia by BMS in an already restenotic lesion (25,27,30). The even more malignant neointimal proliferation seen in diabetes is the likely explanation why neither DES nor BMS benefited this population in our study.

Taken in totality, both the previous indirect analysis by Alfonso et al and our direct comparison with long term follow-up, support the superiority of DES over BMS in treating bare-metal ISR. However for patients needing urgent non-cardiac surgery or those who cannot tolerate prolonged dual antiplatelet therapy, BMS still may be a reasonable alternative to DES particularly in larger vessels.

Our study has several limitations. It is an observational study; therefore, unobserved biases may have played a role in our findings. Future RCT should better address such biases. Some differences were noted amongst the 2 groups and these may have played a role in the benefit seen with DES. However, multiple adjustments for over 23 variables were performed that should have accounted for these baseline differences. Our study population extends to a time when DES were not available, but subgroup analysis revealed that similar results were obtained regardless of the study period examined. One possible mechanism of benefit favoring DES treated patients is a prolonged course of dual antiplatelet therapy in this group. Although data regarding long-term dual antiplatelet therapy is not available, at our institution most operators prescribe 6 weeks of dual antiplatelet therapy for BMS and at least 2 years of dual antiplatelet therapy for DES.

Conclusion

Our study sheds new light on the outcomes of bare-metal ISR treatment with DES versus BMS. In this large cohort of patients with long term follow-up, we demonstrate that there is a considerable and durable advantage of DES over BMS in the treatment of bare-metal ISR. Given the cost, potential for stent thrombosis, and the need for dual antiplatelet therapy, RCT should directly compare DES versus BMS for treating bare-metal ISR.

Acknowledgments

Dr. Shishehbor is supported in part by the National Institutes of Health, National Institute of Child Health and Human Development, Multidisciplinary Clinical Research Career Development Programs Grant K12 HD049091 and the National Institutes of Health Loan Repayment Program.

Dr. Ellis discloses the following relationships: Research Grants - Boston Scientific; Consultant - Boston Scientific, Abbott Vascular, Cordis.

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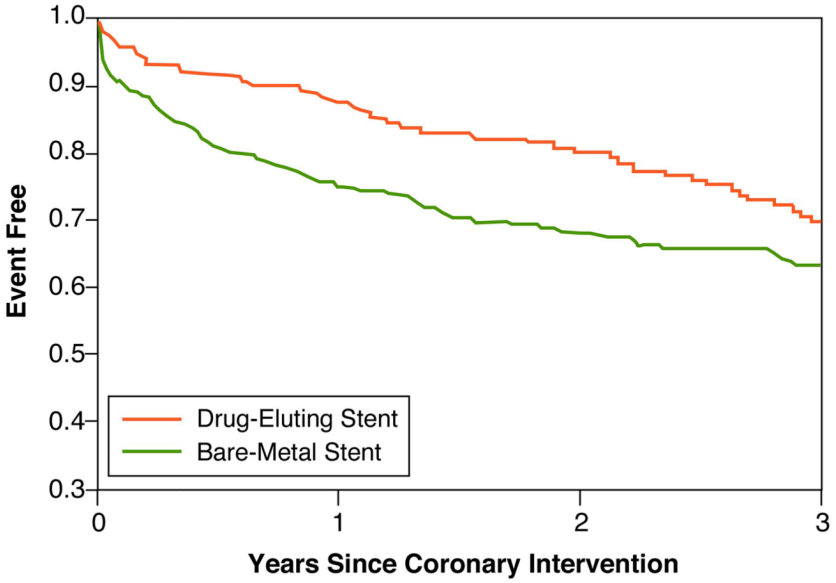

No. at Risk:				
Drug-Eluting Stent	362	222	148	78
Bare-Metal Stent	344	210	177	152

Figure.

Kaplan Meier curves of bare-metal ISR treated with DES versus BMS (n = 706). The composite endpoint of death, myocardial infarction, or target lesion revascularization is represented as a function of time and favors DES. ISR = in-stent restenosis; DES = drug-eluting stents; BMS = bare-metal stents.

Table 1

Baseline and procedural characteristics based on stent used for treating bare-metal in-stent restenosis.

Characteristics	Drug-eluting Stent (n = 362)	Bare-metal Stent (n = 344)	p-value
Age, years	64±11	63±12	0.21
Male, %	271 (75)	229 (67)	0.02
Body mass index	30±5	30±6	0.35
Heart rate	70±14	71±13	0.25
Left ventricular ejection fraction	51±10	51±11	0.67
Risk factors, %			
Family history of premature coronary disease	110 (30)	138 (40)	0.007
Cigarette smoking	38 (11)	42 (12)	0.47
Diabetes mellitus	144 (40)	160 (47)	0.07
Insulin dependent diabetes mellitus	47 (13)	67 (20)	0.02
Non-insulin dependent diabetes mellitus	95 (26)	88 (26)	0.84
Medical history, %			
Prior myocardial infarction	197 (54)	191 (56)	0.77
Peripheral arterial disease	53 (15)	43 (13)	0.41
Prior coronary artery bypass surgery	159 (44)	127 (37)	0.06
Stroke or transient ischemic attack	44 (12)	38 (11)	0.65
Chronic obstructive pulmonary disease	45 (12)	35 (10)	0.34
Clinical presentation, %			
Acute myocardial infarction	8 (2)	11 (3)	0.42
Unstable angina	170 (47)	210 (61)	0.0002
New York Heart Association class, %			
3	46 (13)	11 (3)	<0.0001
4	31 (9)	5 (1)	<0.0001
Medications, %			
Aspirin	362 (100)	344 (100)	1.00
Clopidogrel	362 (100)	344 (100)	1.00
Heparin	111 (31)	192 (56)	<0.0001
Glycoprotein IIb/IIIa inhibitors	107 (30)	258 (75)	<0.0001
Beta-blockers	129 (36)	114 (33)	0.49
Angiotensin converting enzyme inhibitors	182 (50)	134 (39)	0.003
Statins	298 (82)	183 (53)	<0.0001
Location of culprit lesion, %			
Proximal left anterior descending artery	51 (14)	67 (19)	0.06
Mid or distal left anterior descending artery	160 (44)	167 (49)	0.25
Left circumflex artery	158 (44)	141 (41)	0.48
Right coronary artery	153 (42)	177 (51)	0.01
Angiographic characteristics			
Reference vessel diameter, mm	3.0±0.4	2.9±0.5	<0.0001
Stent length, mm	37.7±21.8	20.2±15.8	<0.0001

Characteristics	Drug-eluting Stent (n = 362)	Bare-metal Stent (n = 344)	p-value
Chronic total occlusion, %	30 (8)	12 (3)	0.007
Saphenous vein graft, %	59 (16)	48 (14)	0.39
Multivessel intervention	104 (29)	135 (39)	0.003
Number of diseased vessels, %			
1	225 (62)	147 (43)	<0.0001
2	96 (27)	122 (35)	0.01
3	41 (11)	75 (22)	0.0002
American College of Cardiology lesion score, %			
A	13 (4)	24 (7)	0.04
B1	55 (15)	83 (24)	0.003
B2	115 (32)	112 (33)	0.82
C	179 (49)	125 (36)	0.0004
Procedural success, %	356 (98)	334 (97)	0.27

Table 2

Unadjusted and multivariable adjusted hazard ratios for the primary and secondary endpoints by treatment strategy for bare-metal in-stent restenosis (drug-eluting stents versus bare-metal stents).

	Drug-eluting stent Events (%)	Bare-metal stent Events (%)	Hazard Ratio (95% CI)	p-value
Total Population (n=706)	**n=362**	**n=344**		
Composite of death, MI, or TLR (n=230)	76 (21)	154 (45)	-	-
Unadjusted	-	-	0.69 (0.52-0.92)	0.01
Adjusted	-	-	0.63 (0.42-0.95)	0.03
All cause mortality (n=112)	29 (8)	83 (24)	-	-
Unadjusted	-	-	0.48 (0.31-0.75)	0.001
Adjusted	-	-	0.37 (0.18-0.74)	0.005
Myocardial infarction (n=36)	10 (3)	26 (8)	-	-
Unadjusted	-	-	0.49 (0.23-1.03)	0.06
Adjusted	-	-	0.54 (0.16-1.78)	0.31
Target lesion revascularization (n=116)	47 (13)	69 (20)	-	-
Unadjusted	-	-	0.72 (0.49-1.05)	0.09
Adjusted	-	-	0.67 (0.35-1.29)	0.23

CI = Confidence interval; MI = Myocardial infarction; TLR = Target lesion revascularization.

Table 3

Multivariable adjusted hazard ratios for composite of death, myocardial infarction, or target lesion revascularization in selected sub-groups.

	Drug-eluting stent Events (%)	Bare-metal stent Events (%)	Hazard Ratio (95% CI)	p-value
PCI after 2003 (n=421)	76 (21)	29 (49)	0.59 (0.35-1.00)	0.05
Diabetes Mellitus	-	-	-	-
Present (n = 304)	35 (24)	78 (49)	0.93 (0.51-1.71)	0.83
Absent (n = 402)	41 (19)	76 (41)	0.52 (0.29-0.93)	0.03
Vessel diameter	-	-	-	-
≥ 3.5 mm (n = 112)	11 (17)	23 (48)	0.77 (0.17-3.54)	0.73
< 3.5 mm (n = 594)	65 (22)	131 (44)	0.63 (0.40-0.97)	0.04
Lesion length	-	-	-	-
≥15 mm (n = 336)	44 (23)	68 (47)	0.67 (0.35-1.28)	0.22
< 15 mm (n = 370)	32 (19)	86 (43)	0.66 (0.37-1.19)	0.17

CI = Confidence interval; PCI = Percutaneous coronary intervention.