Simultaneous Drug-Eluting and Bare-Metal Stent Implantation: Long-Term Clinical Outcome and Findings of Clinically Indicated Coronary Angiography

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ABSTRACT

Background: Simultaneous drug-eluting stent (DES) and bare-metal stent (BMS) implantation is occasionally employed in clinical practice, but its long-term clinical and angiographic outcome is not clear.

Hypothesis: We aimed to describe the long-term clinical outcome and the findings of clinically indicated coronary angiography in patients subjected to simultaneous DES and BMS implantation (“hybrid stenting”).

Methods: We identified 236 patients (mean age 62.9 ± 11.4 years, 76.7% men) who had undergone percutaneous coronary intervention with at least 1 DES and 1 BMS. At a median follow-up of 42 months (range, 6–89 months) available in 222 patients, 13 (5.9%) patients died from cardiac causes, 13 (5.9%) experienced nonfatal acute myocardial infarction, and 24 (10.8%) experienced unstable angina. Clinically indicated repeat coronary angiography was performed in 64 patients (28.8%).

Results: Thirty-one patients (14%) had target lesion revascularization (TLR). The DES demonstrated lower TLR rates (15.9% vs 36.9%, $P = 0.002$) and lower late loss (0.44 ± 0.5 mm vs 0.68 ± 0.7 mm, $P = 0.009$) compared with BMS. Use of DES was independently associated with lower risk for binary restenosis (hazard ratio [HR]: 0.41, 95% confidence interval [CI]: 0.19–0.89, $P = 0.03$) and TLR (HR: 0.26, 95% CI: 0.12–0.54, $P < 0.001$).

Conclusions: Although a hybrid stenting strategy demonstrates a reasonable long-term prognosis even in high-risk patients, DES have a better angiographic outcome compared with BMS under the influence of common patient-related restenosis risk factors.

Introduction

There is wide evidence that drug-eluting stents (DES) reduce restenosis rates compared with bare-metal stents (BMS).¹ However, simultaneous implantation of at least 1 DES and 1 BMS in the same patient is occasionally performed.² The study of angiographic outcomes of such a “hybrid stenting” population is of particular interest, as the implanted stents are at least theoretically under the influence of the same patient related risk factors for restenosis. Additionally, the clinical outcome of the hybrid stenting practice is not well-defined, as it has been examined by only a few studies thus far, with both supporters and opponents.^{3–5} Therefore, we conducted a retrospective analysis of clinical and angiographic outcomes of patients with hybrid stenting in our tertiary cardiology service.

Methods

Our cardiac catheterization laboratory database was queried for patients subjected to percutaneous coronary intervention (PCI) with hybrid stenting between June 2002 and December 2008. All patients were treated with aspirin 100 mg/d before PCI and indefinitely thereafter. Clopidogrel was prescribed for a minimum of 3 months following implantation of sirolimus-eluting stents (SES) and 6 months following implantation of paclitaxel-eluting stents for all patients treated before 2006, and for at least 1 year for those treated thereafter. Clinical follow-up data were obtained by review of hospital records and by telephonic contact of all patients. Major adverse cardiac events (MACE) were recorded, including cardiac death, nonfatal myocardial infarction (MI; diagnosed using clinical, electrocardiographic, and biomarker criteria), unstable angina, and stable angina and/or inducible ischemia. Follow-up angiograms were available only for patients who were catheterized on the basis of clinical indications. Initial and follow-up angiograms were evaluated independently by 2 investigators (D.A. and P.D.). Each pair of angiograms was

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Table 1. Baseline Demographic and Procedural Characteristics

	Total Population (n = 236)	Patients Without Repeat Angiogram (n = 172)	Patients With Repeat Angiogram (n = 64)	P Value ^a
Age, y	62.9 ± 11.4	62.6 ± 11.4	63.7 ± 11.5	0.5
Male sex	181 (76.7)	138 (80.2)	43 (67.2)	0.04
DM	105 (44.5)	73 (42.4)	32 (50.0)	0.3
Hypertension	154 (65.3)	113 (65.7)	41 (64.1)	0.9
Hypercholesterolemia	142 (60.2)	106 (61.6)	37 (57.8)	0.7
Current or former smoking	123 (52.1)	94 (34.7)	29 (45.3)	0.2
Family history	49 (20.8)	34 (19.8)	15 (23.4)	0.6
Prior CABG	12 (5.1)	9 (5.2)	3 (4.7)	1
Prior CAD	59 (25)	41 (23.8)	18 (28.1)	0.5
Reason for initial intervention				
Ischemia in provocative test	25 (10.6)	21 (12.2)	4 (6.3)	0.2
Stable angina	42 (17.8)	27 (15.7)	15 (23.4)	0.2
UA	82 (34.7)	55 (32.0)	27 (42.2)	0.2
MI	87 (36.9)	69 (40.1)	18 (28.1)	0.1
Vessels with disease at initial intervention				
1	66 (27.9)	52 (30.2)	14 (21.9)	0.3
2	101 (42.8)	71 (41.3)	30 (46.9)	0.5
3	69 (29.3)	49 (28.5)	20 (31.2)	0.7
Treated vessels at initial intervention				
1	118 (50.0)	90 (52.3)	28 (43.8)	0.3
2	101 (42.8)	73 (42.5)	28 (43.8)	0.9
3	17 (7.2)	9 (5.2)	8 (12.4)	0.08

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; DM, diabetes mellitus; MI, myocardial infarction; SD, standard deviation; UA, unstable angina.

Values are expressed as mean ± SD or n (%).

^aP refers to comparison between patients without angiographic follow-up and those with subsequent clinically driven coronary angiography.

assessed on 2 laptops side by side, or on a laptop and a Tagarno 35AX projector (Tagarno A/S, Horsens, Denmark) in cases where the first angiogram had been recorded on a film. Quantitative coronary angiography measurements were performed blindly to the type of stent, using a CAAS 2000 (Pie Medical Imaging, Maastricht, The Netherlands) or electronic caliper (Yansen Digital Caliper, 66-220; Central Tools Inc., Cranston, RI) for angiograms recorded on a film.

Table 2. Baseline Lesions' Characteristics of Patients With Available Follow-Up (N = 222)

	Lesions Treated With DES (n = 274)	Lesions Treated With BMS (n = 268)	P Value
Total stent length (mm)	20.7 ± 10.5	17.4 ± 7.7	<0.001
Stent diameter (mm)	2.9 ± 1.0	3.0 ± 1.7	0.5
No. of stents (per lesion)	1.1 ± 0.4	1.2 ± 0.5	0.3
Stenosis (%)	60.8 ± 12.8	59.4 ± 12.3	0.2
MLD pre (mm)	0.96 ± 0.4	0.98 ± 0.4	0.6
RD (mm)	2.49 ± 0.7	2.44 ± 0.7	0.4
Lesion length (mm)	13.5 ± 4.7	12.5 ± 4.6	0.02
MLD post (mm)	2.25 ± 0.4	2.29 ± 0.7	0.4
Acute gain (mm) ^a	1.28 ± 0.5	1.24 ± 0.4	0.3
Lesion B2/C type	176 (64.2)	142 (53.0)	0.009
Restenotic lesion	17 (6.2)	1 (0.4)	<0.001
Total occlusion	30 (10.9)	24 (9.0)	0.5
Bifurcation	18 (6.6)	6 (2.2)	0.02
Lesion location			
LM	1 (0.4)	0 (0)	1
LAD	171 (62.4%)	107 (39.9%)	<0.001
LAD proximal	78 (28.5)	38 (14.2)	<0.001
LCX	32 (11.7)	55 (20.5)	0.007
RCA	70 (25.5)	106 (39.6)	0.001

Abbreviations: BMS, bare-metal stent; DES, drug-eluting stent; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; MLD, minimum luminal diameter; RCA, right coronary artery; RD, reference diameter; SD, standard deviation.

Values are expressed as mean ± SD or n (%).

^aAcute gain = MLD post – MLD pre.

Access to the catheterization laboratory database and subsequent analysis were approved by the institutional ethical and research board.

Definitions

A significant lesion was defined as a luminal diameter stenosis ≥50%. Binary restenosis was defined as ≥50%-diameter stenosis, located within the stent, or 5 mm proximal or distal to the stent. Target lesion revascularization (TLR) was defined as repeat PCI or coronary artery bypass grafting due to restenosis, performed ≥30 days after the index procedure. Data regarding binary restenosis and TLR were derived from patients subjected to a new coronary angiography due to clinical indications, and were compared on a per-lesion basis according to the type of stent implanted. Late luminal loss was calculated as postprocedural minimal luminal diameter (MLD) – follow-up MLD. Acute gain was calculated as postprocedural MLD – preprocedural MLD.

Figure 1. Clinical follow-up data. Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Loss index was defined as the ratio of late luminal loss and acute gain. Net gain was calculated as follow-up MLD – preprocedural MLD. Lesion data were recorded according to the American College of Cardiology criteria.⁶

Statistical Analysis

The Student *t* test and Mann-Whitney *U* test were used to compare continuous variables with normal and skewed distribution, respectively, and the Fisher exact test was used for comparison of categorical data. Survival analysis was performed by the Kaplan-Meier method and the curves were compared with the log-rank test. The type of stent used and lesion characteristics at the index procedure for patients subjected to repeat coronary angiogram were considered as factors in a multivariate Cox proportional hazards model using a backward stepwise conditional fashion. Results are expressed as hazard ratios (HR) with 95% confidence intervals (CI). All tests were 2-tailed and statistical significance was set to $P < 0.05$. All statistical analyses were performed using SPSS for Windows, version 16.0 (SPSS Inc., Chicago IL).

Results

Out of 5883 patients who underwent PCI with stenting between June 2002 and December 2008 in our institution,

in 236 (4%) at least 1 BMS and 1 DES were implanted simultaneously. Follow-up data were available for 222 patients (94.1%), who comprised the population of this analysis. In these patients, 268 BMS and 274 DES were implanted in 542 separate lesions. Reasons for simultaneous BMS and DES implantation, as documented in the patients' files, included preference for BMS in 27/268 (10.2%) lesions with presumed low significance (ie, side branches, non-left anterior descending [LAD] lesions) mainly for reducing costs, implantation of a BMS in 91/268 lesions (33.9%) due to unavailability of an optimally sized DES, and implantation of a BMS in 150/268 (55.9%) lesions due to nondeliverability of a chosen DES (ie, excessive tortuosity or calcification). The latter group included 1 patient with initial restenosis in whom a BMS was implanted due to nondeliverability of the DES in a very tortuous artery.

The baseline demographic and procedural characteristics of patients with hybrid stenting are summarized in Table 1 and the lesions' baseline angiographic characteristics in patients with available follow up in Table 2. An SES, Cypher (Cordis Corporation, Miami Lakes, FL), was implanted in 70.5% of DES-treated lesions. Clinical follow-up data are presented in Figure 1. Patients who died on follow-up had 13 DES and 15 BMS implanted, and due to the retrospective nature of the study, no follow-up angiography

Table 3. Lesions' Characteristics of Patients Subjected to Repeat Angiography (N = 64)

	Lesions Treated With DES (n = 88)	Lesions Treated With BMS (n = 84)	P Value
MLD (mm)	1.80 ± 0.6	1.49 ± 0.7	0.02
RD (mm)	2.4 ± 0.5	2.3 ± 0.6	0.02
Stenosis (%)	25.7 ± 19.8	35.2 ± 24.6	0.006
Length (mm)	3.57 ± 1.98	5.1 ± 3.6	0.01
Late lumen loss ^a	0.44 ± 0.5	0.68 ± 0.7	0.009
Late loss index ^b	0.37 ± 0.4	0.52 ± 0.4	0.02
Net gain ^c	0.83 ± 0.6	0.52 ± 0.5	0.001
Binary restenosis	14 (15.9)	24 (28.6)	0.07
A/B1 strata	6 (6.8)	2 (2.4)	0.3
B2/C strata	8 (9.1)	22 (26.2)	0.004

Abbreviations: BMS, bare-metal stent; DES, drug-eluting stent; MLD, minimal lumen diameter; RD, reference diameter; SD, standard deviation.

Values are expressed as mean ± SD or n (%).

^aLate lumen loss = MLD post – MLD follow-up.

^bLate loss index = late loss/acute gain.

^cNet gain = MLD follow-up – MLD pre.

was available. In the 64 patients who were subjected to repeat angiography, at a median time of 18 months (range, 0.2–75 mo), binary restenosis rates were marginally lower in DES compared with BMS (14/88 [15.9%] vs 24/84 [28.6%], respectively, $P = 0.07$). In the B2/C type of lesion strata, binary restenosis rates were significantly lower in DES compared with BMS (8/88 [9.1%] DES vs 22/84 [26.2%] BMS, $P = 0.004$). No such difference was observed in type A/B1 lesions. The lesions' characteristics at repeat angiography are summarized in Table 3. The Kaplan-Meier plot of cumulative incidence of TLR for DES- and BMS-treated lesions is shown in Figure 2. Use of DES was independently associated with lower risk for binary restenosis (hazard ratio [HR]: 0.41, 95% confidence interval [CI]: 0.18–0.89, $P = 0.03$) and TLR (HR: 0.26, 95% CI: 0.12–0.54, $P < 0.001$), whereas longer and in-stent restenotic lesions at initial angiogram increased the risk for TLR (HR: 1.1, 95% CI: 1.02–1.16, $P = 0.01$ and HR: 3.3, 95% CI: 1.09–9.89, $P = 0.03$, respectively).

When we analyzed TLR rates for the total population of 209 alive patients (514 lesions), the results were not different. The TLR rate was lower for lesions treated with DES compared with BMS (13/261 [5.0%] vs 30/253 [11.6%], $P = 0.006$). Multivariate analysis showed that use of DES was independently associated with lower risk for TLR (HR: 0.30, 95% CI: 0.15–0.62, $P = 0.001$) and B2/C type and in-stent restenotic lesions increased the risk for TLR (HR: 2.24, 95% CI: 1.12–4.49, $P = 0.023$ and HR: 4.46, 95% CI: 1.45–13.73, $P = 0.009$, respectively).

Additionally, between January 2004 and December 2008, 360 patients with available follow-up and similar risk factors with our “mixed stent” cohort had ≥ 2 DES implanted (2.42 ± 0.75 stents per patient) in our institution, and

during a period of approximately 30 months the cumulative incidence of MACE was 35.3% (5.3% death, 4.4% MI, 7.2% unstable angina, and 18.3% stable angina and/or inducible ischemia). Target lesion revascularization was performed in 18 (5%) of these patients.

Discussion

Several randomized clinical trials have demonstrated a persistent decrease in the rates of angiographic and clinical restenosis following DES implantation, compared with BMS.¹ In cases of multilesion PCI, when ≥ 1 lesion is treated with a DES, implantation of DES to all the remaining lesions is the usual practice. However, in the “real world,” simultaneous DES and BMS implantation is occasionally employed. In our study, reasons for simultaneous DES and BMS implantation included primarily logistics and procedure-related issues, like preference for BMS due to unavailability of an optimally sized DES in the laboratory, and inability to implant the DES chosen by the interventionist, usually in the case of first-generation DES and/or in severely calcified or tortuous vessels.

Our study presents very-long-term clinical outcomes of such a hybrid stenting population, which additionally demonstrated a high clinical risk profile for restenosis: 44.5% of the patients had diabetes; 42.8% and 29.3% had 2- and 3-vessel disease, respectively; and 50% underwent multivessel stenting. Despite these unfavorable characteristics, a hybrid stenting strategy demonstrates a reasonable long-term prognosis, as our patients overall experienced lower mortality rates compared with large-population cohort studies.^{2,7} Additionally, although not meticulously matched to our study population, results derived from our database for patients with exclusive implantation of ≥ 2 DES show a similar MACE rate.

On the other hand, despite “biases” in favor of BMS-treated lesions like shorter and non-LAD lesions, and under common patient-related factors influencing restenosis, a significant difference in follow-up MLD, late loss, and TLR rates in favor of DES-treated lesions was documented in our study population, whereas our “exclusive” DES population demonstrated a TLR rate of only 5%.

Comparison With Previous Studies

Hybrid stenting remains controversial, with both supporters and opponents of this strategy. Chu et al compared hybrid stenting in patients undergoing multilesion PCI, with the exclusive implantation of DES.³ At 6 months' follow-up, all clinical outcomes were similar between the 2 groups. Also, Bertrand et al reported similar rates of cardiovascular events in the hybrid and exclusive DES strategies at 14 months.⁴ These studies support the idea that hybrid stenting could be considered a viable option for selected patients, and our clinical outcomes would support this view. In contrast, Fineschi et al propose that hybrid stenting should not be considered an effective alternative to exclusive SES use, and BMS use should be limited to cases of unavailability or nondeliverability of the appropriate SES.⁵ More recently, Mirabella et al presented 24 months of follow-up data on 186 patients treated with hybrid stenting. Angiographic follow-up was available in 70.4% of their patients at 8.6 months,

Figure 2. Kaplan-Meier curves presenting the TLR cumulative incidence in 64 patients subjected to repeat angiogram, on a per-lesion basis according to stent type. Abbreviations: BMS, bare-metal stent; DES, drug-eluting stent; TLR, target lesion revascularization.

and the rates of binary restenosis were 12.9% for DES and 20.6% for BMS. However, the superiority of DES compared with BMS was obvious only in complex lesions.⁸ Our results are in accord with these observations regarding angiographic outcomes.

Study Limitations

Our study has several limitations, including a single-center nonrandomized design, heterogeneity in the reason for referral for the first revascularization procedure, the variable duration of antiplatelet treatment, and a nonpredefined protocol for follow-up, with complete clinical follow-up data in 94.1% of patients. Presentation of results regarding patients with exclusive implantation of ≥ 2 DES, although supportive of our conclusion that a mixed stenting strategy has reasonable long-term results, was not in the context of a case-control design. Finally, although 70% of the DES used were Cypher stents, the remaining 30% included different stents, eluting different drugs.

Conclusion

Although a hybrid stenting strategy demonstrates a reasonable long-term outcome overall, DES continue to perform better over BMS under the influence of the same patient-related restenosis risk factors. Application of such a strategy should be reserved only for cases of DES unavailability or nondeliverability.

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