Impact of severe coronary disease associated or not associated with diabetes mellitus on outcome of interventional treatment using stents: Results from HERZ (heart research group of Kanazawa) analyses

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Impact of Severe Coronary Disease Associated or Not Associated with Diabetes Mellitus on Outcome of Interventional Treatment Using Stents: Results from HERZ (Heart Research Group of Kanazawa) Analyses

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Percutaneous coronary intervention (PCI) using a drug-eluting stent (DES) leads to less re-stenosis than PCI using a bare metal stent (BMS), however there is still controversy whether use of a DES for severe coronary disease leads to an acceptable outcome in patients with diabetes mellitus (DM). In this study 8159 lesions were treated in 6739 patients (mean age 68.9 years) with coronary artery disease. Use of a DES significantly decreased the re-stenosis rate compared with BMS in both DM (9.6% versus 21.3%) and non-DM (9.5% versus 17.1%) patients. The re-stenosis rate was significantly higher in DM than in non-DM patients in the BMS group but not in the DES group. There was no statistically significant difference in event-free survival after stenting of patients with left main coronary artery (LMCA) disease between the BMS and DES groups. It was concluded that, compared with BMS, DES reduced re-stenosis in patients with DM, however, we advise careful treatment after using DES for severe coronary disease, including LMCA lesions, in patients with DM.

KEY WORDS: Percutaneous coronary intervention; Drug-eluting stent; Bare metal stent; Coronary artery disease; Left main coronary artery disease; Diabetes mellitus; Major adverse cardiovascular events; Clinical outcome

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Introduction

Introduced about a decade after coronary artery bypass grafting, percutaneous coronary intervention (PCI) has come to be preferred, because it is less invasive, and it is now widely used to treat coronary artery disease.[1,2] Technological improvements, especially the development of coronary stents, have made it possible to treat complex lesions.[3 – 5] However, in previous randomized trials coronary artery bypass grafting was superior to PCI for patients with diabetes or multivessel coronary artery disease when using plain balloon angioplasty or a bare metal stent (BMS).[6,7] The differences in outcome between coronary artery bypass grafting and PCI were mainly associated with re-stenosis of the treated lesions and target lesion revascularization (TLR).

The recent advent of drug-eluting stents (DES) has dramatically reduced the rate of re-stenosis after PCI, and DES are particularly superior to BMS in PCI for small vessels, whether or not the coronary disease is associated with diabetes mellitus (DM). Several trials, however, have demonstrated that DES did not reduce subsequent rates of major adverse clinical events or mortality, although they did reduce the rate of target lesion revascularization compared with the use of a BMS.[8,9] The objective of the present study was to evaluate the clinical outcomes of PCI with a stent in the presence and absence of DM in Japanese patients with coronary artery disease.

Patients and methods

PATIENTS, SUCCESS CRITERIA AND TREATMENTS

Consecutive patients who underwent PCI for coronary artery disease at Kanazawa University Hospital and affiliate hospitals (see Appendix for a list of affiliate hospitals) between January 2006 and December 2008 were eligible for enrolment into the study. The indications for PCI included stable angina pectoris, unstable angina and acute myocardial infarction. Patients who underwent PCI but were treated without stenting, using only balloon dilatation, thrombectomy or directional coronary atherectomy, were excluded.

All procedural decisions, including device selection and adjunctive pharmacotherapy, were made at the discretion of the individual PCI operator. Intravascular ultrasonography was used at the operator's discretion. Procedural (angiographic) success was defined as residual stenosis of < 25%. The definition of clinical success included angiographic success and the in-hospital absence of acute myocardial infarction, congestive heart failure and cardiac death. Procedural and clinical success were evaluated at the time the patient was discharged.

All patients who underwent PCI with a stent received dual antiplatelet therapy comprising aspirin (100 mg/day) and clopidogrel (75 mg/day) or ticlopidine (200 mg/day), and continued this therapy for an appropriate period.

This study was certified by the Ethics Committee of Kanazawa University.

CLINICAL FOLLOW-UP

All patients were evaluated clinically during a follow-up visit to the outpatient clinic and were recommended to receive follow-up coronary angiography at least 6 months after the PCI procedure. Angiographic results and clinical symptoms were used to evaluate the clinical outcome. Binary re-stenosis was defined as ≥ 50% stenosis at the target lesion.

The occurrence of major adverse cardiac events (MACE), defined as sudden cardiac death, acute coronary syndrome-related

target lesions and TLR, was recorded. Coronary risk factors, comprising DM (fasting blood glucose > 126 mg/dl or glycated haemoglobin > 6.5%), hypertension (blood pressure > 130/85 mmHg), hypercholesterolaemia (total cholesterol > 220 mg/dl) and smoking, were also checked and evaluated for association with re-stenosis.

STATISTICAL ANALYSES

Continuous variables were expressed as mean ± SD and were compared using Student's *t*-test and analysis of variance. Categorical data were compared using the χ^2 test or Fisher's exact test. MACE-free survival distributions were calculated by Kaplan–Meier analysis and differences were assessed using the log-rank test. A *P*-value < 0.05 was considered statistically significant. All data analyses were performed using StatView® J 5.0 software (SAS Institute, Cary, NC, USA).

Results

A total of 7660 consecutive patients (5745 men) with 9392 lesions underwent PCI for coronary artery disease at Kanazawa University Hospital and affiliate hospitals between January 2006 and December 2008 and were eligible for enrolment into this study. Angiography was carried out in 5570 (72.7%) of these patients. Of the 9392 total number of lesions, 1233 were treated without stenting (959 using only balloon dilatation and 274 with thrombectomy or directional coronary atherectomy) so were excluded from the analysis. The remaining 8159 lesions in 6739 patients (mean ± SD age 68.9 ± 10.5 years; 5103 men) were evaluated and stenting was successful in 8129 (99.6%) lesions from 6709 (99.6%) patients. Because this was a multicentre study, with data obtained from many hospitals (see Appendix), it was not possible to obtain data on all variables for all patients.

TABLE 1:
Baseline clinical and angiographic characteristics in patients treated with a bare metal stent (BMS) or drug-eluting stent (DES) for coronary artery disease

Characteristic	BMS	DES	Statistical significance
No. of patients	2934	3805	NS
No. of lesions treated by PCI	3536	4623	NS
Acute coronary syndrome, No. (%) of total lesions	1702 (48.1)	719 (15.6)	$P < 0.0001$
Age, years, mean ± SD	68.8 ± 11.2	69.0 ± 10.0	NS
Male, *n* (%)	2230 (76.0)	2873 (75.5)	NS
Coronary risk factors, *n* (%)			
Diabetes mellitus	1171 (39.9)	1899 (49.9)	$P < 0.0001$
Hypertension	1810 (61.7)	2473 (65.0)	NS
Hypercholesterolaemia	1338 (45.6)	1750 (46.0)	NS
Current smoker	1229 (41.9)	1564 (41.1)	NS
Lesion characteristics, *n* (%)			
Single vessel	1623 (55.3)	1925 (50.6)	NS
Two vessels	760 (25.9)	1176 (30.9)	NS
Three vessels	428 (14.6)	590 (15.5)	NS
LMCA	123 (4.2)	114 (3.0)	NS

Percentages calculated on the number of patients unless stated otherwise.
PCI, percutaneous coronary intervention; LMCA, left main coronary artery; NS, not statistically significant, $P > 0.05$.

BASELINE CHARACTERISTICS

Baseline clinical and angiographic characteristics of the patients are shown in Table 1 and were similar in the BMS and DES groups with the exceptions of the number of lesions in patients with acute coronary syndrome (ACS) and the numbers of patients with DM as a coronary risk factor. A total of 2421 lesions were associated with ACS: 1702 (48.1%) and 719 (15.6%) BMS- and DES-treated lesions, respectively ($P < 0.0001$). DM was associated with 3070 patients: 1171 (39.9%) BMS-treated patients and 1899 (49.9%) DES-treated patients ($P < 0.0001$).

IN-HOSPITAL OUTCOMES

Angiographic success was obtained in 6618 (98.2%) and clinical success in 6476 (96.1%) patients. Within 30 days after the procedure, stent-related MACE were observed in 74 (1.1%) patients, including 49 (0.7%) deaths and 25 (0.4%) cases of ACS, comprising 21 (0.3%) cases of myocardial infarction and four (0.05%) cases of unstable angina associated with angiographically confirmed subacute stent thrombosis (Table 2). The frequency of MACE up to 30 days after the procedure was significantly higher in the BMS group than in the DES group ($P < 0.0001$).

LONG-TERM OUTCOMES

Re-stenosis and TLR

All cases of successful stenting (8129 lesions from 6709 patients) were clinically followed up for a period of 3 years and 5975 lesions (73.5%) underwent follow-up coronary angiography after the initial procedure (mean ± SD follow-up interval 7.3 ± 4.9 months). The number of lesions for which re-stenosis was carried out was significantly lower in the DES group than in the BMS group: 445 of 4623 (9.6%) lesions versus 661 of 3536 (18.7%) lesions (relative risk 1.94 for the BMS group versus the DES group; $P < 0.01$; Fig. 1). Similarly, the rate of TLR was also significantly lower in the DES group than in the BMS group: 327 of 4623 (7.1%) lesions versus 472 of 3536 (13.6%) lesions (relative risk 1.46 for the BMS group versus the DES group; $P < 0.01$; Fig. 1). The long-term cumulative frequency of MACE in patients with ACS was similar in the BMS and DES groups: 83/1702 (4.9%) and 26/719 (3.6%) patients, respectively.

TABLE 2:
In-hospital and long-term cumulative major adverse cardiovascular events (MACE) in patients treated with a bare metal stent (BMS) or drug-eluting stent (DES) for coronary artery disease

Variable	BMS ($n = 2934$)	DES ($n = 3805$)	Statistical significance
No. of lesions treated by PCI	3536	4623	
In-hospital MACE[a]			$P < 0.0001$
Death, *n* (%)	40 (1.4)	9 (0.2)	$P < 0.0001$
Acute coronary syndrome	12 (0.4)	13 (0.3)	NS
Long-term cumulative MACE[b]			NS
Death, *n* (%)	39 (1.3)	24 (0.6)	NS
Acute coronary syndrome, *n* (%)	20 (0.7)	26 (0.7)	NS
TLR (% of total lesions)	472 (13.3)	327 (7.1)	NS

[a]In-hospital data refer to an interval of up to 30 days after the PCI procedure.
[b]Long-term data refer to the interval from 1 month to 1 year after percutaneous coronary intervention (PCI).
TLR, target lesion revascularization; NS, not statistically significant, $P > 0.05$.

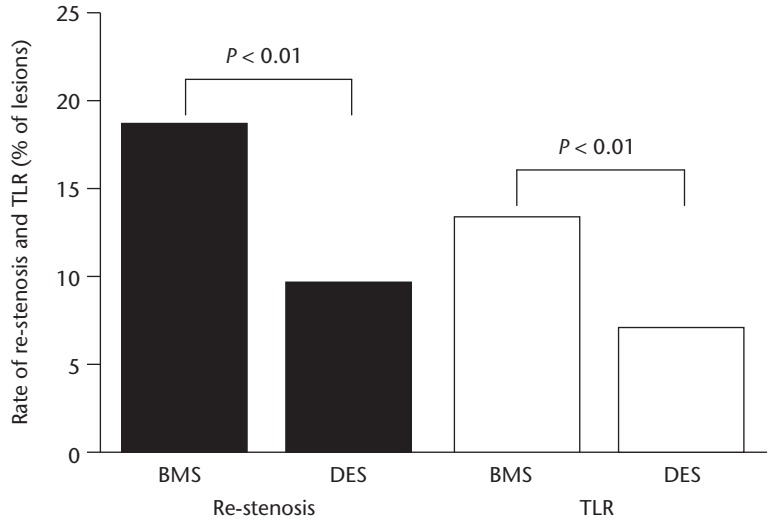

FIGURE 1: Rates of re-stenosis and target lesion revascularization (TLR) in patients treated with a bare metal stent (BMS) or a drug-eluting stent (DES) for coronary artery disease, determined on angiography at follow-up (mean ± SD follow-up interval 7.3 ± 4.9 months)

Subgroup analysis of re-stenosis

The overall in-stent re-stenosis rate was significantly ($P < 0.05$) greater in patients with DM (553/3070 patients; 18.0%) than in patients without DM (587/3669 patients; 16.0%). There was, however, no statistically significant effect of DM on the re-stenosis rate in the DES group (182/1899 patients [9.6%] with DM compared with 181/1906 patients without DM [9.5%]) whereas DM did have a statistically significant effect in the BMS group (249/1171 patients [21.3%] with DM compared with 301/1763 patients without DM [17.1%]; $P < 0.01$) (Fig. 2). There was no significant effect of other coronary risk factors with regard to the occurrence of re-stenosis.

Event-free survival analysis

Evaluation of event-free survival after stenting was examined in the BMS and DES groups by Kaplan–Meier analysis (Fig. 3). In one- and two-vessel disease, event-free survival decreased until about 200 and 300 days after stenting in patients treated with BMS and DES, respectively, and was significantly higher in the DES group than in the BMS group ($P < 0.001$). In three-vessel disease, event-free survival was also higher in the DES group than in the BMS group ($P < 0.001$) and the pattern of the Kaplan–Meier survival curves was similar to that of one- and two-vessel disease. In terms of patients fitted with a DES, event-free survival did not differ significantly between patients with one- or two-vessel disease and those with three-vessel disease, however, among patients treated with a BMS the long-term outcome of three-vessel disease was significantly worse than that of one- or two-vessel disease ($P < 0.001$). Event-free survival also decreased until 200 and 300 days after stenting of patients with LMCA disease in the BMS and DES groups, respectively, but the eventual survival rate did not differ significantly between these two groups.

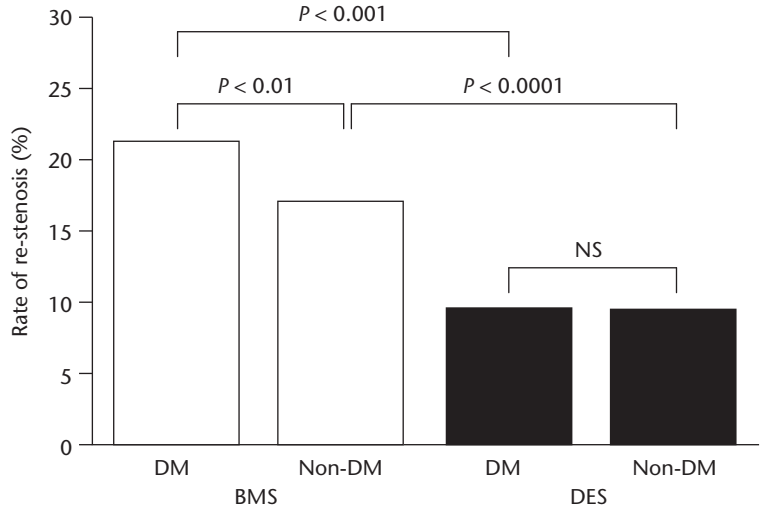

FIGURE 2: Re-stenosis rate 3 years after treatment with a bare metal stent (BMS) or a drug-eluting stent (DES) for coronary artery disease in patients with and without diabetes mellitus (DM) (NS, not statistically significant, $P > 0.05$)

Among patients with LMCA disease, event-free survival was significantly higher in those with non-bifurcation lesions (76/82 patients; 92.7%) than in those with bifurcation lesions (124/155 patients; 80.0%) ($P = 0.0433$). The outcome of LMCA lesions treated with a BMS or DES was worse than that of non-LMCA lesions and survival with

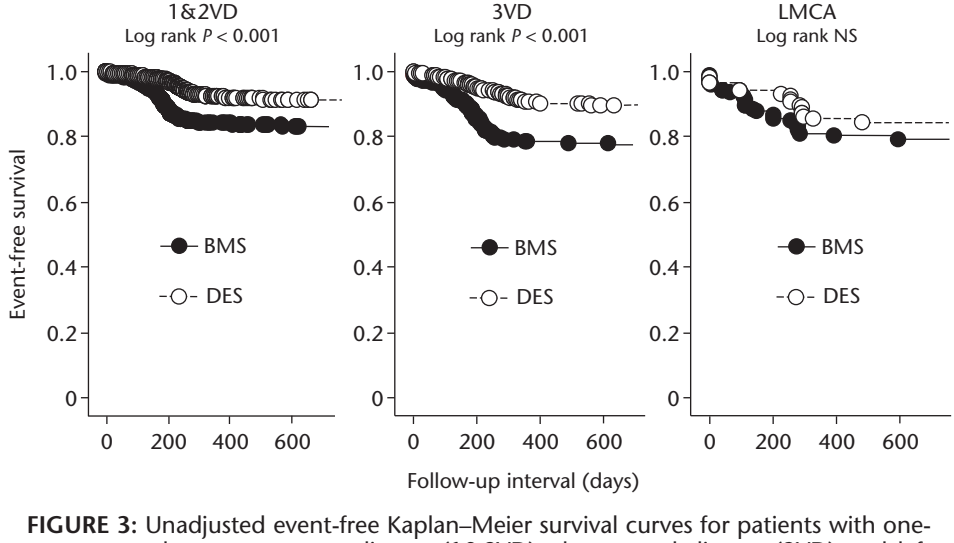

FIGURE 3: Unadjusted event-free Kaplan–Meier survival curves for patients with one- or two-vessel coronary artery disease (1&2VD), three-vessel disease (3VD) and left main coronary artery (LMCA) disease treated with a bare metal stent (BMS) or drug-eluting stent (DES) (NS, not statistically significant, $P > 0.05$)

a DES was superior to that with a BMS in patients with non-LMCA lesions (data not shown).

Discussion

The present study revealed that PCI in a real-world population was safe and feasible, with an angiographic procedural success rate of 98.2%, and the BMS and DES treatments were associated with low rates of MACE. Although the in-hospital MACE rate in the BMS group was significantly ($P < 0.0001$) higher than that in the DES group, this was considered to be because of the significantly higher incidence of patients with ACS who were treated with a BMS. There was no significant difference in MACE between the two groups when comparison was restricted only to patients showing ACS after stenting.

Implantation of a DES could reduce the risk of TLR by 40%, although it might also carry a minor risk of stent thrombosis and myocardial infarction within 2.7 years compared with BMS implantation.[10,11] In the present study, the relative risk of TLR following BMS implantation was 1.46 that of DES, however there were no differences between DES and BMS in the long-term risks of MACE (death, myocardial infarction or unstable angina associated with stent thrombosis). This may be explained by the fact that intravascular ultrasound and continuous dual antiplatelet therapy were frequently used.

It has been shown that DM is one of the most substantial risk factors for re-stenosis after stent implantation, with odds ratios of 1.9 – 2.5.[12] In the present study, using a DES led to a decrease in the rate of TLR compared with using a BMS, particularly in patients with DM. This result was consistent with a previous study in which TLR rates associated with a DES, during 4 years of follow-up, were 9.7% and 8.7% for patients with and without DM, respectively, and rates associated with a BMS were 22.4% and 16.4%, respectively.[13] Re-stenotic intimal hyperplasia in patients with DM may differ from that in patients without DM in terms of cellular aspects.[14,15] For example, diabetic vascular smooth muscle cells have been shown to exhibit increased rates of proliferation, leading to luminal narrowing.[14] A polymer coating, that releases anti-inflammatory and antiproliferative agents, is used in DES[15] and this may effectively prevent intimal proliferation in patients with or without DM.[16] We have reported previously that the use of a DES could suppress out-stent plaque progression, which was closely related to the progression of intimal hyperplasia[17] and this effect may be particularly relevant in the presence of DM.

The late outcome of one- and two-vessel disease, three-vessel disease and LMCA disease after DES and BMS implantation was evaluated in the present study. Event-free survival did not differ significantly between patients with one- or two-vessel disease and those with three-vessel coronary disease treated with a DES however, among patients treated with a BMS, the long-term outcome of three-vessel disease was worse than that of one- or two-vessel disease, probably because multivessel disease is often associated with multiple coronary risk factors.[18]

The outcome of LMCA lesions treated with a BMS or DES was worse than that of non-LMCA lesions. Although the eventual survival rate was not significantly different between the BMS and DES groups in LMCA disease, survival in patients fitted with a DES was superior to those with BMS in patients with non-LMCA lesions. Differences were particularly notable in bifurcation lesions. It is commonly thought that stenting for bifurcation lesions is associated with a high re-stenosis rate and this might have a

considerable impact on clinical survival.[19] We consider, therefore, that LMCA lesions should not be treated by DES implantation alone but additionally with interventions such as coronary artery bypass grafting, or by combining PCI with bypass surgery.

The present study had several limitations. First, because it was not randomized, the results might have been influenced by potential biases, however a relatively large number of patients (> 5000) were examined which may have minimized the effect of this limitation. Secondly, access to all information about the patients' medications, except for the antiplatelet agents used, was not available. This may have had some influence on the results, particularly regarding the long-term outcome. Indeed, several studies have reported different conclusions, suggesting superiority of the DES over the BMS in LMCA lesions.[20 – 23] Further large prospective trials, in which the effects of several coronary risk factors and lesion characteristics, especially LMCA lesions, are considered, may demonstrate differences between DES and BMS in severe coronary lesions, including those of the LMCA.

This evaluation of the clinical outcomes treated with stents in a real-world population of patients with coronary artery disease in Japan showed that the use of a DES dramatically decreased the rate of re-stenosis compared with the use of a BMS, particularly in patients with DM. However, very late re-stenosis was observed in a few cases treated with a DES, probably because of delayed healing of the stenting lesion. There was no statistically significant difference in event-free survival after stenting of patients with LMCA disease between the BMS and DES groups. We suggest careful treatment after using DES for severe coronary disease, including LMCA lesions, in patients with DM.

Appendix

The following hospitals in Japan, are affiliated with Kanazawa University Hospital: Kanazawa Cardiovascular Hospital, Fukui Cardiovascular Centre, Maizuru Kyousai Hospital, Ishikawa Prefectural Central Hospital, Toyama Red Cross Hospital, Yokohama Sakae Kyousai Hospital, Takaoka City Hospital, Komatsu Municipal Hospital, Fukui Prefectural Hospital, Koseiren Takaoka Hospital, Kaga Municipal Hospital, Houju Memorial Hospital, Saiseikai Kanazawa Hospital, Kanazawa Social Insurance Hospital, KKR Hokuriku Hospital.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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References

1 Favaloro RG: Saphenous vein autograft replacement of severe segmental coronary artery occlusion: operative technique. *Ann Thorac Surg* 1968; **5:** 334 – 339.
2 Gruntzig A: Transluminal dilatation of coronary-artery stenosis. *Lancet* 1978; **i:** 263.
3 Palmaz JC: Balloon-expandable intravascular stent. *AJR Am J Roentgenol* 1988; **150:** 1263 – 1269.
4 Serruys PW, de Jaegere P, Kiemeneij F, *et al* for the Benestent Study Group: A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994; **331:** 489 – 495.
5 Ormiston JA, Dixon SR, Webster MW, *et al*: Stent longitudinal flexibility: a comparison of 13 stent designs before and after balloon expansion. *Catheter Cardiovasc Interv* 2000; **50:**

120 – 124.
6 Niles NW, McGrath PD, Malenka D, *et al* for the Northern New England Cardiovascular Disease Study Group: Survival of patients with diabetes and multivessel coronary artery disease after surgical or percutaneous coronary revascularization: results of a large regional prospective study. *J Am Coll Cardiol* 2001; **37:** 1008 – 1015.
7 Kimura T, Morimoto T, Furukawa Y, *et al*: Long-term outcomes of coronary-artery bypass graft surgery versus percutaneous coronary intervention for multivessel coronary artery disease in the bare-metal stent era. *Circulation* 2008; **118(14 suppl):** S199 – S209.
8 Jensen LO, Tilsted HH, Thayssen P, *et al*: Paclitaxel and sirolimus eluting stents versus bare metal stents: long-term risk of stent thrombosis and other outcomes. From the Western Denmark Heart Registry. *EuroIntervention* 2010; **5:** 898 – 905.
9 Park DW, Kim YH, Yun SC, *et al*: Long-term outcomes after stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 10-year results of bare-metal stents and 5-year results of drug-eluting stents from the ASAN–MAIN (ASAN Medical Center–Left MAIN Revascularization) Registry. *J Am Coll Cardiol* 2010; **56:** 1366 – 1375.
10 Auer J, Leitner A, Berent R, *et al*: Long-term outcomes following coronary drug-eluting- and bare-metal-stent implantation. *Atherosclerosis* 2010; **210:** 503 – 509.
11 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 – 1019.
12 Airoldi F, Briguori C, Iakovou I, *et al*: Comparison of sirolimus versus paclitaxel eluting stents for treatment of coronary in-stent restenosis. *Am J Cardiol* 2006; **97:** 1182 – 1187.
13 Stettler C, Allemann S, Wandel S, *et al*: Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. *BMJ* 2008; **337:** a1331.
14 Moreno PR, Murcia AM, Palacios IF, *et al*: Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. *Circulation* 2000; **102:** 2180 – 2184.
15 Lexis CP, Rahel BM, Meeder JG, *et al*: The role of glucose lowering agents on restenosis after percutaneous coronary intervention in patients with diabetes mellitus. *Cardiovasc Diabetol* 2009; **8:** 41.
16 Airoldi F, Briguori C, Iakovou I, *et al*: Comparison of sirolimus versus paclitaxel eluting stents for treatment of coronary in-stent restenosis. *Am J Cardiol* 2006; **97:** 1182 – 1187.
17 Tada H, Kawashiri MA, Sakata K, *et al*: Impact of out-stent plaque volume on in-stent intimal hyperplasia: result from serial volumetric analysis with high-gain intravascular ultrasound. *Int J Cardiol* 2011; epub ahead of print.
18 Serruys PW, Morice MC, Kappetein AP, *et al*: Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; **360:** 961 – 972.
19 Sheiban I, Sillano D, Biondi-Zoccai G, *et al*: Incidence and management of restenosis after treatment of unprotected left main disease with drug-eluting stents: 70 restenotic cases from a cohort of 718 patients: FAILS (Failure in Left Main Study). *J Am Coll Cardiol* 2009; **54:** 1131 – 1136.
20 Chieffo A, Stankovic G, Bonizzoni E, *et al*: Early and mid-term results of drug-eluting stent implantation in unprotected left main. *Circulation* 2005; **111:** 791 – 795.
21 Valgimigli M, van Mieghem AG, Ong ATL, *et al*: Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: insights from the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH and T-SEARCH) registries. *Circulation* 2005; **111:** 1383 – 1389.
22 Park SJ, Kim YH, Lee BK, *et al*: Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. *J Am Coll Cardiol* 2005; **45:** 351 – 356.
23 Gao R, Xu B, Chen J, *et al*: Immediate and long-term outcomes of drug-eluting stent implantation for unprotected left main coronary artery disease: comparison with bare-metal stent implantation. *Am Heart J* 2008; **155:** 553 – 561.

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