Outcomes of DES in Diabetic and Nondiabetic Patients with Complex Coronary Artery Disease after Risk Stratification by the SYNTAX Score

Mohamed Loutfi, Mohamed A. Sadaka and Mohamed Sobhy

Cardiology Department, Alexandria University, Alexandria, Egypt.

ABSTRACT

Diabetes mellitus (DM) increases the risk of adverse outcomes after coronary revascularization. Controversy persists regarding the optimal revascularization strategy for diabetic patients with multivessel coronary artery disease (MVD).

AIM: The aim of this study was to assess the outcomes of drug-eluting stent (DES) insertion in DM and non-DM patients with complex coronary artery disease (CAD) after risk stratification by the percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score.

METHODS AND RESULTS: We performed multivessel percutaneous coronary intervention (PCI) for 601 lesions in 243 DM patients and 1,029 lesions in 401 non-DM patients. All included patients had MVD and one or more lesions of type B2/C. The two-year outcomes and event rates were estimated in the DM and non-DM patients using Kaplan–Meier analyses. The baseline SYNTAX score was ≤22 in 84.8% vs. 84%, $P = 0.804$, and 23–32 in 15.2% vs. 16%, $P = 0.804$, of the DM and non-DM patients, respectively. The number of diseased segments treated (2.57 ± 0.75 vs. 2.47 ± 0.72; $P = 0.066$) and stents implanted per patient (2.41 ± 0.63 vs. 2.32 ± 0.54; $P = 0.134$) were similar in both groups. After a mean follow-up of 642 ± 175 days, there were no differences in the major adverse cardiac and cerebrovascular events (MACCE; 26.7% vs. 20.9%; $P = 0.091$), composite end point of all-cause death/myocardial infarction (MI)/stroke (12.3% vs. 9%; $P = 0.172$), individual MACCE components of death (3.7% vs. 3.2%; $P = 0.754$), MI (6.6% vs. 4%; $P = 0.142$), and absence of stroke in the DM and non-DM patients. An increased need for repeat revascularization was observed in DM patients (18.5% vs. 10.2%; $P = 0.003$). In the multivariate analysis, DM was an independent predictor of repeat revascularization (hazard ratio: 1.818; 95% confidence interval: 1.162–2.843; $P = 0.009$).

CONCLUSIONS: DES implantation provides favorable early and mid-term results in both DM and non-DM patients undergoing PCI for complex lesions. After a mean follow-up of two years, DM and non-DM patients with complex CAD treated by PCI using new-generation DES showed no differences with regard to MACCE and other secondary end points. However, higher rates of ischemia-driven repeat revascularization were observed in DM patients.

KEYWORDS: diabetes mellitus, drug-eluting stent(s), prognosis

CITATION: Loutfi et al. Outcomes of DES in Diabetic and Nondiabetic Patients with Complex Coronary Artery Disease after Risk Stratification by the SYNTAX Score. *Clinical Medicine Insights: Cardiology* 2016:10 103–110 doi: 10.4137/CMC.S37239.

TYPE: Original Research

RECEIVED: November 03, 2015. **RESUBMITTED:** February 02, 2016. **ACCEPTED FOR PUBLICATION:** February 05, 2016.

ACADEMIC EDITOR: Thomas E. Vanhecke, Editor in Chief

PEER REVIEW: Three peer reviewers contributed to the peer review report. Reviewers' reports totaled 775 words, excluding any confidential comments to the academic editor.

FUNDING: Authors disclose no external funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

CORRESPONDENCE: drmloutfi@gmail.com

Introduction

In the last several decades, the global prevalence of diabetes mellitus (DM) has continuously increased.[1,2] Coronary artery disease (CAD) is a major cause of morbidity and mortality in diabetic patients, and more than 80% of DM deaths occur in low- and middle-income countries.[3,4] Compared to non-diabetic patients, patients with DM have a greater extent of coronary atherosclerosis, higher plaque burden,[5] and are more prone to develop multivessel CAD.[6,7]

Coronary artery revascularization in patients with DM poses a challenge because diabetes has been found to increase the risk of adverse outcomes after coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).[8–10] The current guidelines recommend CABG over PCI in patients with DM and multivessel coronary artery disease (MVD) CAD.[11,12] The FREEDOM trial demonstrated that CABG was superior to multivessel PCI with the use of first-generation drug-eluting stents (DESs) in patients with DM and MVD. CABG significantly reduced the rates of death and myocardial infarction (MI) but was associated with a higher rate of nonfatal stroke.[13] Although CABG remains superior to PCI among patients with DM and MVD, particularly for patients with higher angiographic disease complexity, the gap between CABG and PCI has narrowed over time.[14] Future trial should be performed to compare CABG and the new PCI technologies based on the currently available newer generation stents specifically in diabetic patients to define the optimal management strategy.

The percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score is an angiographic scoring tool used for systematically quantifying the severity and assessing the characteristics of individual coronary lesions.[15] This score is used worldwide to predict the long-term outcomes in patients with CAD undergoing elective PCI or CABG surgery. The SYNTAX score (SS) was shown to be an independent predictor of long-term adverse outcomes in patients with multivessel disease undergoing PCI.[16]

Aim

The aim of this study was to assess the outcomes of DES implantation in DM and non-DM patients with complex CAD after risk stratification by the SS.

Methods

Study population. From June 2012 to June 2013, a total of 644 consecutive patients (243 DM patients with 601 treated lesions and 401 non-DM patients with 1,029 treated lesions) were included. All patients underwent early PCI during their admission at Alexandria Main University Hospital and the International Cardiac Center (ICC) at Alexandria.

Inclusion criteria. All included patients had MVD and ≥1 lesion with an American College of Cardiology (ACC) and American Heart Association (AHA) classification type B2/C[17] with clinical indications for revascularization who had not previously undergone angioplasty or coronary surgery. Multivessel PCI was systematically offered to the patients as an alternative to surgery whenever complete revascularization with a finite number of stents was judged to be feasible.

Exclusion criteria. Patients were excluded based on the following criteria:

- Patients with multivessel disease who were candidates for CABG (SS ≥ 33),
- Patients with left main disease,
- Patients with previous PCI,
- Patients with previous CABG, and
- Patients with a life-threatening noncardiac illness.

Procedural data. All patients who underwent PCI received at least 300 mg of aspirin and a 600-mg loading dose of clopidogrel. Heparin was administered throughout the procedure to maintain an activated clotting time of ≥250 seconds. The DES selection and use of glycoprotein IIb/IIIa inhibitors were left to the discretion of the surgeon. After the procedure, all patients received 100 mg/day of aspirin indefinitely, as well as 150 mg of clopidogrel for seven days, followed by 75 mg/day of clopidogrel for at least 12 months. The use of standard postintervention care was recommended.

Angiographic analysis. Angiographic imaging was performed in two orthogonal views after the intracoronary injection of nitrates. Each lesion was measured before and after stenting on nonoptically magnified cineangiographic frames showing the lesion in its highest grade, using the guiding catheter as a reference. Measurements of the diameter of the guiding catheter, the minimal vessel lumen diameter, and the percent stenosis before and after stenting were performed by automatic contour edge detection; intravascular ultrasound imaging was not routinely used. The patients' angiographic images were reviewed, and the SS was calculated using a web-based calculator (www.syntaxscore.com) by the same trained physician, who was blinded to the clinical outcomes of the patients.

Patient follow-up. Clinical follow-up was performed for all patients at 1, 3, 6, 9, and 12 months and every 3 months thereafter either during outpatient department visits or by direct telephone calls to patients. All the patients were contacted for follow-up regarding the presence of angina, adverse events (death, nonfatal MI, and need for repeat percutaneous intervention in the target lesion), and CABG. For all patients who reported cardiac symptoms, a clinical evaluation was performed. Noninvasive testing for myocardial ischemia was performed for all patients unless contraindicated. Follow-up coronary angiography was performed for all patients with a recurrence of angina or positive findings detected by noninvasive testing. All data collected were stored in a regularly updated computer database.

Study outcomes and definitions. The primary outcome of this study was the major adverse cardiac and cerebrovascular events (MACCE) [a composite of the cardiac death, MI, or iischemia driven target lesion revascularization (ID-TLR)], death (cardiac and noncardiac), nonfatal MI, ID-TLR, stent thrombosis, and stroke. Periprocedural MI was defined as an increase of biomarkers (creatine kinase isoenzyme MB [CK-MB] or troponin) greater than three times the upper limit of normal.[18] *Q-wave MI* was defined as an elevation of CK-MB ≥2 times the upper normal value in the presence of new pathologic Q-waves (>0.4 seconds) in ≥2 contiguous leads of the electrocardiogram. *Non-Q-wave MI* was defined as typical ischemic chest pain and/or ST-segment and/or T-wave abnormalities with a CK-MB increase ≥2 times the reference values without any new pathologic Q-waves. *TLR* was defined as clinically driven revascularization of the index lesion. Stent thrombosis was defined as definite or probable stent thrombosis according to the Academic Research Consortium definitions.[19] DM was defined as either a previous diagnosis of diabetes treated with diet, oral agents, peptide analogs, and insulin or a new diagnosis during index hospitalization.

Statistical analysis. Qualitative data were described using numbers and percentages and were compared using chi-squared test. Quantitative data were described using means and standard deviations as measures of central tendencies and dispersion, respectively, for normally distributed data and were compared using Student's *t*-test, while abnormally distributed data were expressed using medians, minimums, and maximums and were compared using Mann–Whitney test. Cumulative event rates were estimated using time-to-event methods, survival functions were compared using log-rank test, and Kaplan–Meier survival curve was used to illustrate the survival functions. Cox proportional hazards multivariate analysis was performed to adjust for baseline characteristic differences that remained despite the propensity matching. All statistical analyses were performed using the SPSS software (version 20.0; SPSS Inc.). A value of $P < 0.05$ was considered to be statistically significant.

Sample size and power calculation. Using NCSS 2004 and PASS 2000 software (power analysis and sample size), group sample sizes of 243 and 401 (total, 644) achieve 82% power to detect a difference of 10% of the proportion surviving at two years (not developing any MACE event) between the diabetic and nondiabetic groups (0.6 and 0.7, respectively) using log-rank test and using a significance level of 0.05.

Ethics statement. This study was reviewed and approved by the review board of the Faculty of Medicine, Alexandria University. The research complied with the principles of the Declaration of Helsinki. All participants were requested to provide written informed consent regarding the procedure according to the study protocol.

Results

We performed multivessel PCI in 243 DM patients with 601 treated lesions and 401 non-DM patients with 1,029 treated lesions using second-generation DES (everolimus-eluting stents [EES] or zotarolimus-eluting stents). All included patients had MVD and ≥1 lesion of type B2/C. Baseline clinical characteristics of the study groups are shown in (Table 1). The two-year outcomes and event rates were estimated in both groups of patients using Kaplan–Meier analyses.

There was no statistically significant difference between two groups as regards the angiographic characteristics, the baseline SS (Table 2), the number of diseased segments treated (2.57 ± 0.75 vs. 2.47 ± 0.72; $P = 0.066$), and stents implanted per patient (2.41 ± 0.63 vs. 2.32 ± 0.54; $P = 0.134$).

Inhospital outcome. There was no significant difference in the inhospital MACCE between the two groups (2% vs. 2.1%; $P = 1.000$), as shown in Table 3.

Mid-term outcome. After a mean follow-up of 642 ± 175 days, there were no differences in the MACCE (26.7% vs. 20.9%; $P = 0.091$), composite end point of all-cause death/MI/stroke (12.3% vs. 9%; $P = 0.172$), individual MACCE components of death (3.7% vs. 3.2%; $P = 0.754$), MI (6.6% vs. 4%; $P = 0.142$), and absence of stroke in the DM and non-DM patients. A greater need for repeat revascularization was observed in DM patients (18.5% vs. 10.2%; $P = 0.003$), as shown in Table 3. The Kaplan–Meier survival curves based on the MACCE rates, death/MI/stroke and repeat revascularization in diabetic and nondiabetic patients are shown in Figures 1–3.

In the multivariate analysis, DM was identified as the only independent predictor of repeat revascularization even after adjustment of baseline characteristic differences, which was significantly different between the two groups by univariate analysis (hazard ratio: 1.818; 95% confidence interval: 1.162–2.843; $P = 0.009$), as shown in Table 4.

Discussion

DM is becoming one of the most important health problems worldwide. Approximately 60% of all patients who undergo coronary artery revascularization via CABG or PCI have MVD that is amenable to treatment by one of these procedures. The long-term success of multivessel PCI in diabetic patients is principally limited by the need for repeat revascularizations, which are performed not only for restenosis but also for disease progression. This study examined the outcomes of DES implantation in DM and non-DM patients with complex

Table 1. Baseline clinical characteristics.

VARIABLE	NON-DIABETIC (n = 401)		DIABETIC (n = 243)		P VALUE
	NO.	%	NO.	%	
Sex					
Male	347	86.5	192	79.0	0.012*
Female	54	13.5	51	21.0	
Age (years)	56.93 ± 9.48		57.70 ± 9.99		0.329
DM – oral agents	0	0.0	207	85.2	<0.001*
DM-insulin	0	0.0	36	14.8	<0.001*
Hypertension	159	39.7	143	58.8	<0.001*
Dyslipidaemia	212	52.9	131	53.9	0.797
Family history CAD	161	40.01	111	45.7	0.169
Smoking	223	55.6	105	43.2	0.002*
Chronic renal insufficiency	8	2.0	14	5.8	0.011*
Dialysis	0	0.0	2	0.8	0.142
Previous myocardial infarction	59	14.7	36	14.8	0.972
Previous PCI	57	14.2	29	11.9	0.410
Stable angina	45	11.2	33	13.6	0.374
Unstable angina	51	12.7	76	31.3	<0.001*
Silent ischemia	61	15.2	28	11.5	0.189
Post-MI angina	62	15.5	21	8.6	0.012*
Mitral regurgitation	28	7.0	12	4.9	0.297
Aortic stenosis	9	2.2	0	0.0	0.031*
β-blockers	177	44.1	125	51.4	0.072
CCBs	63	15.7	38	15.6	0.980
ACE-I	56	14.0	46	18.9	0.094
LVEF%	60.35 ± 11.85		59.21 ± 11.67		0.234

Notes: Qualitative data were described using numbers and percentages and were compared using chi-squared test. Quantitative data were described using means and standard deviations for normally distributed data and were compared using Student's *t*-test, while abnormally distributed data were expressed using medians, minimums, and maximums and were compared using Mann–Whitney test. *Statistically significant at $P \leq 0.05$.
Abbreviations: ACE-I, angiotensin converting enzyme inhibitors; CCBs, calcium channel blockers; LVEF, left ventricular ejection fraction.

Table 2. Baseline angiographic characteristics.

	NON-DIABETIC (n = 401)		DIABETIC (n = 243)		*P* VALUE
	NO.	%	NO.	%	
Number of diseased vessels					
2	190	47.4	127	52.3	0.230
3	211	52.6	116	47.7	
Number of treated vessels					
2	316	78.8	202	83.1	0.180
3	85	21.2	41	16.9	
Number of treated lesions					
Mean ± SD	2.57 ± 0.75		2.47 ± 0.72		0.066
2	224	56	154	63.4	0.315
3	134	33.5	69	28.4	
4	31	7.8	14	5.8	
5	11	2.8	6	2.5	
Number of stents/patient					
Mean ± SD	2.41 ± 0.63		2.32 ± 0.54		0.134
2	266	66.5	174	71.6	0.363
3	108	27	60	24.7	
4	24	6	9	3.7	
5	2	0.5	0	0.0	
Glycoprotein IIb/IIIa inhibitors	44	11.2	29	12.0	0.749
Guiding catheter	6.05 ± 0.22		6.04 ± 0.27		0.741
Angiographic success	398	99.3	242	99.6	0.668
Follow-up (days; mean = 542.01)	522		590		0.002*
Syntax score	17.29 ± 4.81		17.02 ± 4.80		0.484
<23	337	84	206	84.8	0.804
≥23	64	16	37	15.2	
Days to event	446.5 (1–960)		450 (1–956)		0.875

Notes: Qualitative data were described using numbers and percentages and were compared using chi-squared test. Quantitative data were described using means and standard deviations for normally distributed data and were compared using Student's *t*-test, while abnormally distributed data were expressed using medians, minimums, and maximums and were compared using Mann–Whitney test. *Statistically significant at $P \leq 0.05$.

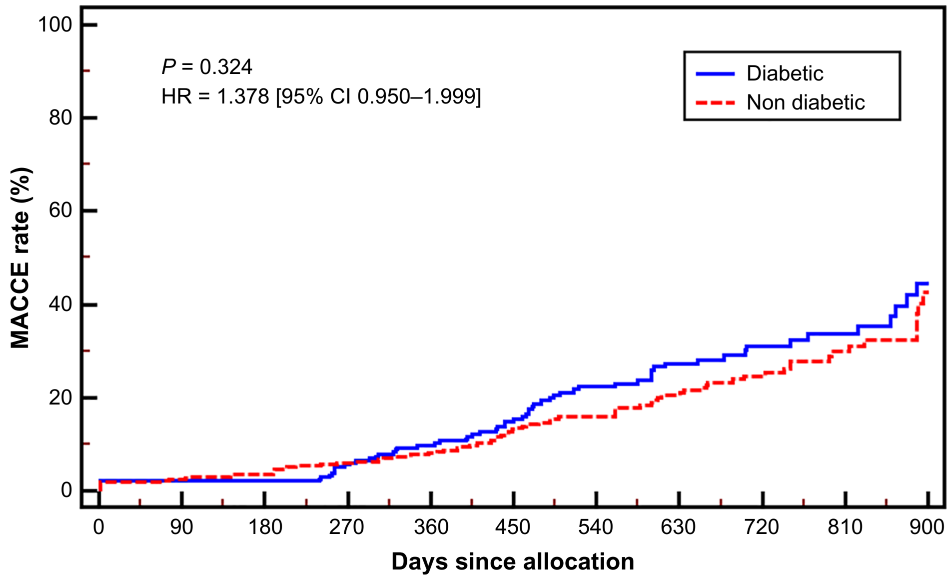
Table 3. Inhospital and mid-term outcomes according to the diabetic status.

	NON-DIABETIC (n = 401)		DIABETIC (n = 243)		*P* VALUE
	NO.	%	NO.	%	
In-hospital MACCE	8	2.0	5	2.1	1.000
TVR	0	0.0	1	0.4	0.377
Death	1	0.2	1	0.4	1.000
MI	6	1.5	5	2.1	0.755
MI (STEMI)	2	0.5	1	0.4	1.000
MI (Non-STEMI)	4	1.0	5	2.1	0.309
Stroke	1	0.2	1	0.4	1.000
FU-MACCE (two-year)	76	19.0	60	24.7	0.084
Death	13	3.2	9	3.7	0.754
Cardiac	10	2.5	7	2.9	0.767
Non-cardiac	3	0.7	2	0.8	1.000
MI	16	4.0	16	6.6	0.142
MI (STEMI)	6	1.5	8	3.3	0.130
MI (Non-STEMI)	10	2.5	8	3.3	0.551
Stroke	0	0.0	0	0.0	–
Repeat revascularization	41	10.2	45	18.5	0.003*
PCI	36	9.0	41	16.9	0.003*
CABG	5	1.2	4	1.6	0.735
Death/MI/stroke	36	9.0	30	12.3	0.172
All MACCE	84	20.9	65	26.7	0.091

Notes: Qualitative data were described using numbers and percentages and were compared using chi-squared test. *Statistically significant at $P \leq 0.05$.

CAD after risk stratification by the SS. The baseline SS was ≤22 in 84.8% DM patients vs. 84% in non-DM patients, while 15.2% vs. 16% of the DM and non-DM patients, respectively, had an intermediate SS (23–32). After two years of follow-up, there were no differences in the rates of MACCE (26.7% vs. 20.9%), composite end point of all-cause death/MI/stroke (12.3% vs. 9%), individual MACCE components of death (3.7% vs. 3.2%), MI (6.6% vs. 4%), and absence of stroke in the DM and non-DM patients. The present study, representing a patient population with a broad spectrum of clinical presentations varying from stable angina pectoris to ST-segment elevation MI, demonstrates that DM was associated with a higher need for repeat revascularization in DM patients (18.5% vs. 10.2%; $P = 0.003$), even with the use of DES.

The selection of an appropriate revascularization strategy for an individual patient with MVD is complex. The current guidelines recommend that CABG should be preferred to PCI in patients with MVD and DM.[11,12] The FREEDOM trial demonstrated that in diabetic patients with MVD, CABG was superior to PCI when the first-generation DESs were used. CABG significantly reduced the rates of death and MI but was associated with a higher rate of stroke. Subgroup analyses of DM patients included in the FREEDOM trial stratified by insulin treatment have been reported by Dangas et al. The overall five-year event rate of death/stroke/MI was significantly higher in patients treated with insulin than in those not treated with insulin (28.7% vs. 19.5%; $P < 0.001$).[20] Before the results of the FREEDOM trial are applied to all DM patients in real-world practice, it should be considered that only 10% of the screened patients met the inclusion criteria, with only two-thirds of these finally providing informed consent for participation. In addition, the PCI group comprised a high-risk population: 82% had three-vessel disease, the mean number of lesions/patient was 5.6 ± 2.2, and 34% of the patients were insulin-treated DM patients. In addition, 65% of the PCI patients had an



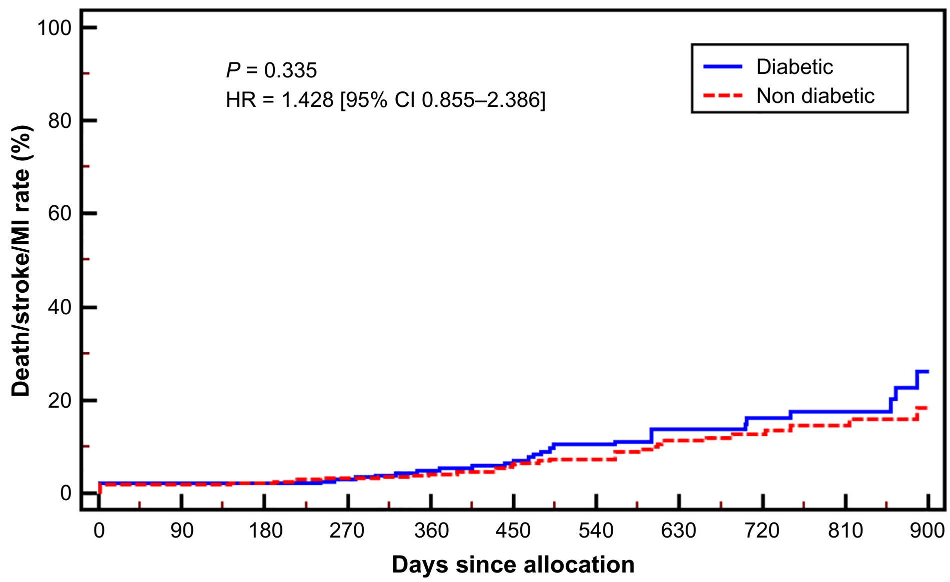
Number at risk

Group	0	90	180	270	360	450	540	630	720	810	900
Group: Diabetic	243	238	236	209	190	157	120	95	66	43	13
Group: Non diabetic	401	362	352	315	272	230	185	141	103	61	22

Figure 1. The Kaplan–Meier survival curves based on the MACCE rates in diabetic and nondiabetic patients.

intermediate or high SS. First-generation DESs were used in 94% of the included patients.

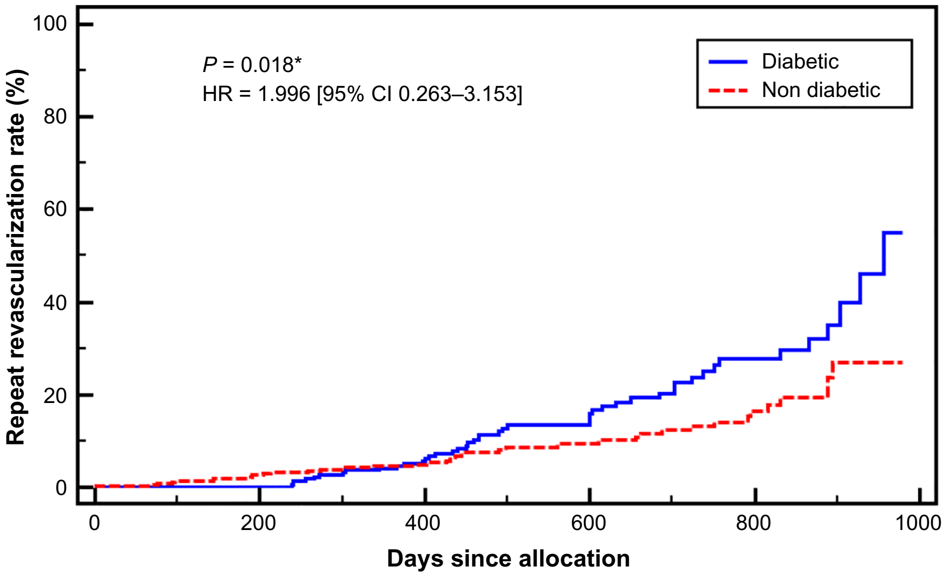
Data based on the conclusions from the CARDia trial[21] and the five-year results of the SYNTAX trial indicated significantly higher rates of MACCE and repeat revascularization in patients with DM treated with PCI compared with those treated with CABG.[16] The SYNTAX trial concluded that PCI is a potential treatment option for patients with less complex lesions, but that CABG should be the revascularization option of choice for patients with more complex anatomical disease, especially in DM patients. Extrapolating the findings of the previous trials to current clinical practice is not



Number at risk

Group	0	90	180	270	360	450	540	630	720	810	900
Group: Diabetic	243	238	236	209	190	157	120	95	66	43	13
Group: Non diabetic	401	362	352	315	272	230	185	141	103	61	22

Figure 2. The Kaplan–Meier survival curves for the death/stroke/MI rates in diabetic and nondiabetic patients.



Number at risk					
Group: Diabetic					
243	231	178	102	43	0
Group: Non diabetic					
401	343	257	153	68	0

Figure 3. The Kaplan–Meier survival curves for the repeat revascularization rates in diabetic and nondiabetic patients.

really possible because the use of the newer generation DES now available may lead to a better outcome in DM patients. The combination of thin struts and the advanced polymer technology of the newer generation DES has been shown to contribute to improved early endothelialization, lower inflammation, and lower stent thrombosis rates.[22,23] A recent study conducted by Pendyala et al showed better safety and efficacy of EES compared with the first-generation DES when used in diabetic patients undergoing multivessel PCI. In DM patients undergoing native multivessel PCI, the use of EES was associated with superior one-year safety compared with the use of first-generation DES. This benefit was mainly driven by decreased rates of all-cause mortality and cardiac mortality in the EES group.[24]

Table 4. Cox proportional hazard multivariate analysis for repeat revascularization.

	P VALUE	HR	95.0% CI	
			LOWER	UPPER
Gender	0.651	1.150	0.628	2.108
Smoking	0.137	1.405	0.898	2.201
Hypertension	0.331	1.244	0.801	1.932
Diabetes mellitus	0.009*	1.818	1.162	2.843
Renal Insufficiency	0.883	1.091	0.340	3.497
Unstable angina	0.231	1.406	0.805	2.456

Notes: Multivariate logistic regression analysis was performed using male gender, smoking, hypertension, DM, renal insufficiency (estimated glomerular filtration rate <60 mL/minute/1.73 m^2), and unstable angina.*Statistically significant at $P \leq 0.05$.
Abbreviations: CI, confidence interval; HR, hazard ratio.

In the present study, multivessel PCI was performed in 243 DM patients with 601 treated lesions and 401 non-DM patients with 1,029 treated lesions. The differences between the study protocol and the previous trials were: (1) all included patients had MVD and ≥1 lesion of type B2/C treated with ≥2 stents in ≥2 different coronary territories (excluding the left main), (2) the majority of the study population (≈84%) had a low SS (≤22) and the maximum SS was ≤27, (3) a small number of the study participants were insulin-treated diabetic patients (14.8%), (4) the reference vessel diameter of all treated lesions was ≥2.75 mm, and (5) the treatments involved the use of new-generation DESs. The two-year outcomes showed a higher need for repeat revascularization in DM patients, but no significant differences with regard to the MACCE, composite end point of all-cause death/MI/stroke, individual MACCE components of death, MI, and absence of stroke. These results with relatively better clinical outcomes in diabetic patients could be explained by the differences in the inclusion criteria, patient selection, and use of newer generation DES.

In agreement with our study, a large analysis of 18 pooled randomized trials examining DES outcomes according to the presence of DM conducted by Kedhi et al.[25] demonstrated that DM remains an independent predictor of one-year repeat revascularization and adverse events (cardiac death or MI) in the DES era. There were increased rates of TLR and target vessel revasularization (TVR) in patients with DM versus those without DM with complex lesions (ACC/AHA class B2/C), but not in patients with simpler lesions (A/B1). However, there was no significant relationship between the presence of diabetes, lesion type, and cardiac death or MI. The main finding of this study was that diabetic patients had favorable intermediate-term outcomes after the treatment of noncomplex lesions with DES. In addition, the two-year results of the international global RESOLUTE program evaluating the outcomes of zotarolimus-eluting stents in 1,535 patients with DM compared with all 3,595 patients without diabetes showed an equivalent cumulative incidence of target lesion failure in patients with noninsulin-treated DM versus patients without DM. The patients with insulin-treated diabetes demonstrated a significantly higher target lesion failure rate. It should be noted that the high-risk subsets from the RESOLUTE All Comers and the observational RESOLUTE international study were excluded from the primary analysis of that study.[26] Moreover, some of the registry data have shown that the clinical events were similar in diabetic patients undergoing CABG surgery or PCI.[27,28] Advances in PCI technology, including newer generation DES and bioabsorbable stents, may further reduce the risk of target lesion failure, the need for repeat revascularization, and the long-term risk of stent thrombosis.[29] Additionally, functional assessment with fractional flow reserve will help identify hemodynamically important and significant lesions that would benefit most from revascularization. Using such a strategy would allow for the identification of ischemia-producing lesions and may have important prognostic utility in reclassifying patients with MVD into functional one- or two-vessel CAD.[30,31]

The findings of the present study demonstrated favorable mid-term outcomes in selected diabetic patients after treatment of complex lesions with the new-generation DES, although there was a greater need for repeat revascularization in the diabetic patients. The optimal revascularization strategy in diabetic patients with MVD must be determined after considering the different anatomical, clinical, and technical factors for each particular patient. All of these factors should be assessed by the heart team in order to make a decision for an individual patient in *real-world* practice. Future clinical trials should compare CABG and the new PCI technologies based on the currently available newer generation stents, specifically in diabetic patients, in order to define the optimal management strategy.

Conclusions

The currently used newer generation DESs are associated with favorable early and mid-term results in both DM and non-DM patients undergoing PCI for complex lesions. After a mean follow-up of two years, DM and non-DM patients with complex CAD treated by PCI using the new-generation DES showed no differences with regard to MACCE and other secondary end points. However, higher rates of ischemia-driven repeat revascularization were observed in DM patients. For patients with DM and complex CAD, the decision to proceed to coronary revascularization must carefully consider and incorporate all of the clinical and angiographic characteristics and the circumstances of each individual patient, and such a decision should be made only after discussion in a multidisciplinary *heart team*.

Study Limitations

This study was a prospective single-center study and therefore lacks randomization and intention to treat data. As an observational study, it is subject to selection bias. The reason for choosing multivessel PCI in preference to CABG was not evaluated in the present study. The study sample was relatively small, and the short duration of follow-up in this study should be considered a limitation of the present analysis. Therefore, our results did not provide data on the outcome of multivessel PCI in DM versus non-DM patients in the longer perspective. Despite these limitations, this study provides insight into a large series of consecutive diabetic patients treated with native multivessel PCI and their mid-term outcomes.

Author Contributions

Conceived and designed the experiments: ML. Analyzed the data: ML. Wrote the first draft of the manuscript: ML, MAS. Contributed to the writing of the manuscript: ML. Agree with manuscript results and conclusions: ML, MAS, MS. Jointly developed the structure and arguments for the paper: ML, MAS, MS. Made critical revisions and approved final version: ML, MAS, MS. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Danaei G, Finucane MM, Lu Y, et al; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Glucose). Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet*. 2011;378:31–40.
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;27:1047–53.
3. World Health Organization, *Fact Sheet No. 312. Diabetes Mellitus*. Available at http://www.who.int/mediacentre/factsheets/fs312/en/. Updated January 2015.
4. World Health Organization. Global Health Estimates: Deaths by Cause, Age, Sex and Country, 2000–2012. Geneva: WHO; 2014.
5. Ibebuogu UN, Nasir K, Gopal A, et al. Comparison of atherosclerotic plaque burden and composition between diabetic and non-diabetic patients by non-invasive CT angiography. *Int J Cardiovasc Imaging*. 2009;25(7):717–23.
6. Holper EM, Abbott JD, Mulukutla S, et al. Temporal changes in the outcomes of patients with diabetes mellitus undergoing percutaneous coronary intervention in the National Heart, Lung, and Blood Institute dynamic registry. *Am Heart J*. 2011;161:397.e–403.e.
7. Natali A, Vichi S, Landi P, Severi S, L'Abbate A, Ferrannini E. Coronary atherosclerosis in Type II diabetes: angiographic findings and clinical outcome. *Diabetologia*. 2000;43:632–41.
8. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet*. 2009;373:1190–7.
9. Roffi M, Angiolillo DJ, Kappetein AP. Current concepts on coronary revascularization in diabetic patients. *Eur Heart J*. 2011;32:2748–57.
10. Onuma Y, Wykrzykowska JJ, Garg S, et al. ARTS I and II Investigators. 5-Year follow-up of coronary revascularization in diabetic patients with multivessel coronary artery disease: insights from ARTS (arterial revascularization therapy study)-II and ARTS-I trials. *JACC Cardiovasc Interv*. 2011;4:317–23.

11. Kolh P, Windecker S, Alfonso S, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35(37):2541–619.
12. Qaseem A, Fihn SD, Dallas P, et al. Clinical guidelines committee of the American College of Physicians. Management of stable ischemic heart disease: summary of a clinical practice guideline from the American College of Physicians/American College of Cardiology Foundation/American Heart Association/American Association for Thoracic Surgery/Preventive Cardiovascular Nurses Association/Society of Thoracic Surgeons. *Ann Intern Med*. 2012;157:735–43.
13. Farkouh ME, Domanski M, Sleeper LA, et al; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012;367:2375–84.
14. Armstrong EJ, Rutledge JC, Rogers JH. Coronary artery revascularization in patients with diabetes mellitus. *Circulation*. 2013;128:1675–85.
15. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005;1:219–27.
16. Kappetein AP, Head SJ, Morice MC, et al. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardiothorac Surg*. 2013;43:1006–13.
17. Ryan TJ, Faxon DP, Gunnar RM, et al. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *Circulation*. 1988;78:486–502.
18. Thygesen K, Alpert JS, White HD, et al; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. ESC/ACCF/AHA/WHF expert consensus document. *J Am Coll Cardiol*. 2007;50:2173–95.
19. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med*. 2007;356:1020–9.
20. Dangas GD, Farkouh ME, Sleeper LA, et al; FREEDOM Investigators. Long-term outcome of PCI versus CABG in insulin and non–insulin-treated diabetic patients: results from the FREEDOM trial. *J Am Coll Cardiol*. 2014;64:1189–97.
21. Kapur A, Hall RJ, Malik IS, et al. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients: 1-year results of the CARDIA (coronary artery revascularization in diabetes) trial. *J Am Coll Cardiol*. 2010;55:432–40.
22. Pendyala LK, Yin X, Li J, Chen JP, Chronos N, Hou D. The first-generation drug-eluting stents and coronary endothelial dysfunction. *JACC Cardiovasc Interv*. 2009;2:1169–77.
23. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. *J Am Coll Cardiol*. 2008;52:333–42.
24. Pendyala L, Loh J, Kitabata H, Chen JP, Chronos N, Hou D. Clinical impact of second-generation everolimus-eluting stents compared with first-generation drug-eluting stents in diabetic patients undergoing multivessel percutaneous coronary intervention. *J Invasive Cardiol*. 2015;27(6):263–8.
25. Kedhi E, Généreux P, Palmerini T, et al. Impact of coronary lesion complexity on drug-eluting stent outcomes in patients with and without diabetes mellitus. Analysis from 18 pooled randomized trials. *J Am Coll Cardiol*. 2014;63:2111–8.
26. Silber S, Serruys PW, Leon MB, et al. Clinical outcome of patients with and without diabetes mellitus after percutaneous coronary intervention with the resolute zotarolimus-eluting stent 2-year results from the prospectively pooled analysis of the International Global RESOLUTE Program. *JACC Cardiovasc Interv*. 2013;6:357–68.
27. Sedlis SP, Morrison DA, Lorin JD, et al; Investigators of the Department of Veterans Affairs Cooperative Study #385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). Percutaneous coronary intervention versus coronary bypass graft surgery for diabetic patients with unstable angina and risk factors for adverse outcomes with bypass: outcome of diabetic patients in the AWESOME randomized trial and registry. *J Am Coll Cardiol*. 2002;40:1555–66.
28. Yan Q, Changsheng M, Shaoping N, et al. Percutaneous treatment with drug-eluting stent vs. bypass surgery in patients suffering from chronic stable angina with multivessel disease involving significant proximal stenosis in left anterior descending artery. *Circ J*. 2009;73:1848–55.
29. Diletti R, Serruys PW, Farooq V, et al. ABSORB II randomized controlled trial: a clinical evaluation to compare the safety, efficacy, and performance of the Absorb everolimus-eluting bioresorbable vascular scaffold system against the XIENCE everolimus-eluting coronary stent system in the treatment of subjects with ischemicheart disease caused by de novo native coronary artery lesions: rationale and study design. *Am Heart J*. 2012;164:654–63.
30. Park SJ, Kang SJ, Ahn JM, et al. Visual-functional mismatch between coronary angiography and fractional flow reserve. *JACC Cardiovasc Interv*. 2012;5:1029–36.
31. Nam CW, Mangiacapra F, Entjes R, et al; FAME Study Investigators. Functional syntax score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol*. 2011;58:1211–8.