



First and second generation DESs reduce diabetes adverse effect on mortality and re-intervention in multivessel coronary disease: 9-Year analysis^{☆,☆☆}



Sanaa A. Badour^a, Kamellia R. Dimitrova^b, Yumiko Kanei^c, Robert F. Tranbaugh^b, Mark M. Hajjar^a, Ameer Kabour^d, Thomas A. Schwann^e, Samir Alam^a, Kamal Badr^a, Robert H. Habib^{a,*}

^a Department of Internal Medicine, Vascular Medicine Program and Outcomes Research Unit, American University of Beirut, Lebanon

^b Divisions of Cardiology, Mount Sinai Beth Israel Medical Center, New York, NY, USA

^c Cardiothoracic Surgery, Mount Sinai Beth Israel Medical Center, New York, NY, USA

^d Division of Cardiology, Mercy Saint Vincent Medical Center, Toledo, OH, USA

^e Department of Surgery, University of Toledo College of Medicine, Toledo, OH, USA

ARTICLE INFO

Article history:

Received 4 November 2016

Received in revised form 23 January 2017

Accepted 27 January 2017

Keywords:

Bare metal stent

Percutaneous coronary intervention

New generation DES

Survival analysis

ABSTRACT

Background/purpose: Diabetes portends an increased risk of adverse early and late outcomes in patients undergoing PCI. In this study, we aimed to investigate if the adverse effect of diabetes mellitus (DM) on early and late PCI outcomes is reduced with drug-eluting (DES) compared to bare-metal (BMS) stents.

Methods/materials: We reviewed the Mount Sinai Beth Israel Hospital first PCI experience for multivessel coronary artery disease (CAD, 1998–2009). Patients were excluded if they had single-vessel CAD, emergency, no stent, prior bypass graft or myocardial infarction <24 h. Diabetes-effect was derived from 9-year all-cause mortality and re-intervention risk-adjusted hazard ratios [AHR (95% confidence intervals)] for DES ($N = 2679$; 48% three-vessel; 39% DM) and BMS ($N = 2651$; 40% three-vessel; 33% DM) and then stratified based on stent (DES/BMS) and vessel disease (two/three).

Results: Diabetes-effect on mortality was lower for DES ($AHR_{DM/NoDM} = 1.41 [1.14–1.74]$) versus BMS ($AHR_{DM/NoDM} = 1.71 [1.50–2.01]$), but this was predominantly driven by two-vessel patients. This diabetes effect was similar for first (DES1: $AHR_{DM/NoDM} = 1.43 [1.14–1.79]$) and second (DES2: $AHR_{DM/NoDM} = 1.53 [0.77–3.07]$) generation DES. Re-intervention comparisons were similarly increased by diabetes in all sub-cohorts.

Conclusions: Our analysis of a large real-world PCI series indicates that diabetes is associated with worse 9-year mortality irrespective of stent type, albeit this is mitigated to varying degrees with DES, particularly in DES2 and in case of 2-vessel disease. A complementary stent-effect analysis confirmed DES-to-BMS and DES2-to-DES1 superiority in both diabetics and non-diabetics.

© 2017 Elsevier Inc. All rights reserved.

1. Introduction

Diabetes mellitus (DM) is a major and rapidly increasing risk factor of cardiovascular disease, that affects one of every three patients undergoing coronary revascularization [1]. Diabetics are generally characterized by increased atherosclerotic burden and, consequently, a greater likelihood of multivessel coronary artery disease (CAD) [2,3]. These features of CAD in diabetes also portend an increased risk of adverse early

and late outcomes following coronary revascularization whether achieved by bypass graft surgery [4,5] or percutaneous coronary intervention (PCI) [6,7].

Anti-proliferative and anti-inflammatory properties of drug eluting intracoronary stents (DES) have effectively led to them replacing bare-metal stent (BMS) as the PCI standard-of-care. Yet, the extent to which DES is effective in reducing the intermediate to late term adverse effects of diabetes on PCI outcomes is incompletely elucidated. Accordingly, this study aimed to assess the hypothesis that DES use attenuates the diabetes adverse effects on long term PCI outcomes in patients with multivessel CAD. Here, we reasoned that the DES-derived benefit will manifest in two complementary and related ways: (1) relatively lower late adverse outcomes' diabetes-related hazard ratios (*Diabetes Effect*) in DES compared to BMS treated patients, and (2) improved late outcomes in diabetic patients treated with DES versus BMS (*Stent Effect*). Toward this, we analyzed early-to-late mortality and re-intervention

[☆] Disclosures: None.

^{☆☆} Funding Sources: (1) SAB was partly supported by a Fogarty training grant awarded to the Scholars in Health Research Program (grant no.: NIH-FIC-D43TW009118). (2) Departmental and institutional funds.

* Corresponding author at: Outcomes Research Unit, Department of Internal Medicine, American University of Beirut Medical Center, PO Box: 11-0236, Riad El Solh, 1107 2020, Beirut, Lebanon. Tel.: +961 1 350000; fax: +961 1 743033.

E-mail address: rh106@aub.edu.lb (R.H. Habib).

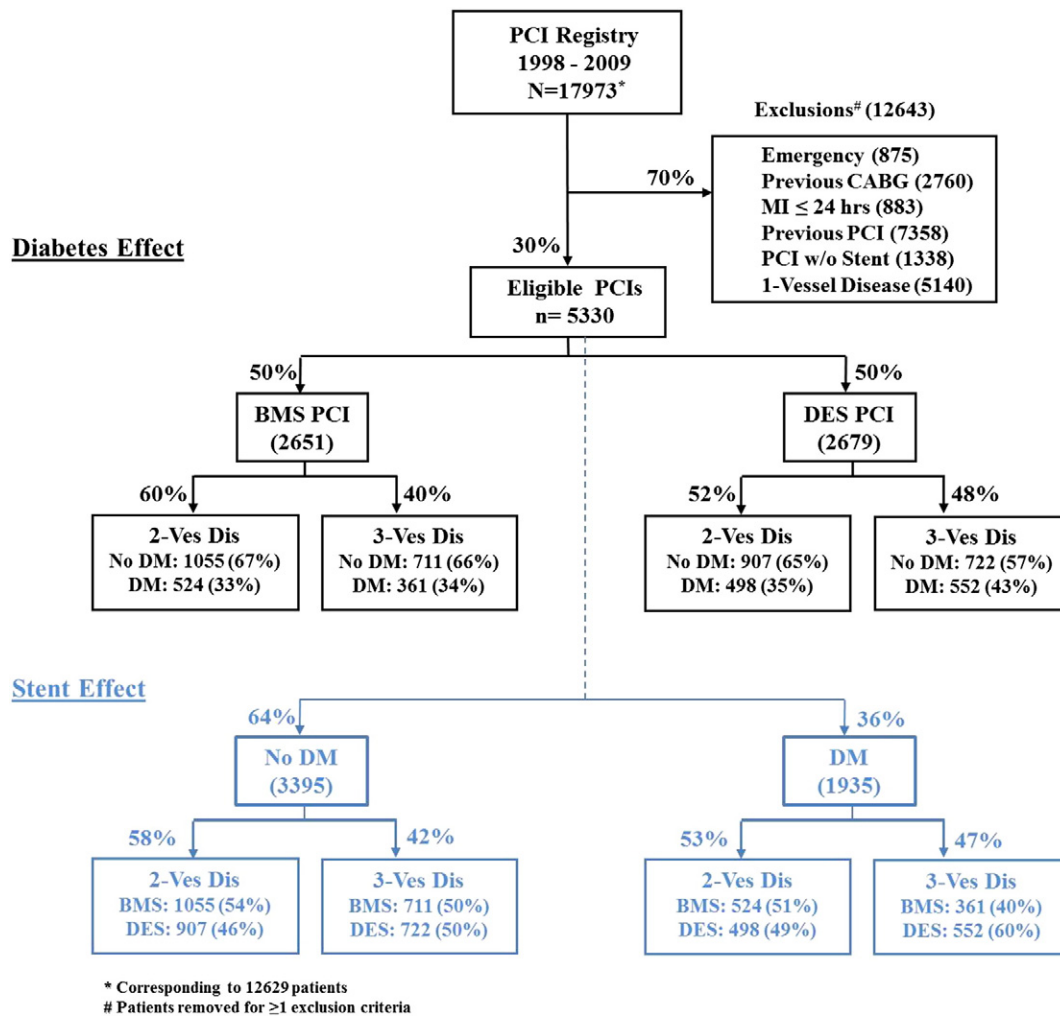


Fig. 1. Flowchart depicting implemented study design and patient stratification.

rates from a large 'real-world' PCI experience in patients with multivessel CAD.

2. Methods

This investigation is a retrospective analysis from the Mount Sinai Beth Israel Medical Center (NY, USA) percutaneous coronary intervention database. The database is collected and reported in accordance with the New York State Department of Health, Division of Quality and Patient Safety Cardiac Services Program. The institutional review board approved the use of these data. The need of an informed consent was waived since no additional review of the hospital records or interviewing of patients was done.

We reviewed the PCI experience between January 1998 and December 2009 (Fig. 1). Consecutive adult patients with multivessel disease undergoing their first, non-emergency PCI were included if they received at least one intracoronary stent. BMS use decreased from 100% of patients in 1998 to 11% in 2009. Alternatively, DES use increased from 59% in 2003 up to 89% in 2009. Multivessel disease was defined as presence of significant stenosis (>50%) in vessels belonging to two or all three of the left anterior descending (LAD), circumflex (LCX) and right coronary artery (RCA) beds. Patients were excluded if they had single vessel disease, underwent emergency PCI, had prior coronary revascularization (PCI or coronary artery bypass grafting, CABG), or had a myocardial infarction within 24 h prior to PCI. A total of 5330 out of 17,973 overall PCI encounters (31%) were retained for analysis. A small number of patients who received both BMS and DES were considered as DES subjects

($n = 102$). Both first (DES1: 2064 (76%) overall; 1386 (51%) paclitaxel/678 (25%) sirolimus) and second (DES2: 615 (24%) overall; 444 (17%) zotarolimus/171 (7%) everolimus) generation DES were used.

Outcomes of interest included 0–9 year survival after PCI and up to 9-year coronary re-intervention rates (PCI or CABG). Pre-planned additional PCIs were considered to be staged interventions and hence were not reflected as re-intervention outcome events. All-cause mortality was obtained from the hospital records and recurrent searches of the Social Security Death Index (last search in 2013). Information about re-intervention was obtained from the institutional cardiology-PCI and cardiac surgery databases (December 31, 2010 only).

Categorical factors were summarized as counts and percentages, whereas continuous variables were reported as mean \pm standard deviation. Univariate comparisons were done with chi-square (χ^2) for categorical factors, and unpaired t -test or Mann–Whitney U test for continuous variables as appropriate based on normality of data. Time-to-event analyses truncated at a maximum of 9 years were calculated using the Kaplan–Meier product limit method to estimate unadjusted survival (or re-intervention) with between-groups comparisons (log-rank test). Analyses were performed to derive within stent type (Diabetes Effect) and within diabetes status (Stent Effect) outcome comparisons based on the multiple stratification of the study population paradigms shown in Fig. 1. The stent or diabetes based strata were further partitioned into 2-vessel and 3-vessel subgroups. The studied effect was derived for each sub-stratum as the risk-adjusted diabetes (AHR_{DM/NoDM} [95% CI]) or the risk-adjusted stent (AHR_{DES/BMS} [95% CI]) hazard ratio with the corresponding 95% confidence interval. AHRs

Table 1Comparison of demographics and risk factors in diabetic (DM) versus non-diabetic (NoDM) sub-cohorts of BMS and DES treated patients^a

	BMS (N = 2651)		DES (N = 2679)	
	NoDM (1766)	DM (885)	NoDM (1629)	DM (1050)
Continuous variables	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
BMI (kg/m ²)	28.0 ± 5.2	30.2 ± 6.1*	28.1 ± 5.3	30.0 ± 6.1*
BSA (m ²)	1.89 ± 0.23	1.93 ± 0.25*	1.89 ± 0.25	1.92 ± 0.24*
Ejection fraction (%)	50.5 ± 11.1	50.3 ± 11.5	53.4 ± 10.2	53.6 ± 10.9
Creatinine (mg/dL)	1.4 ± 1.2	1.3 ± 1.0*	1.0 ± 0.7	1.0 ± 0.7
Categorical variables	n (%)	n (%)	n (%)	n (%)
Male	1210 (69)	485 (55)*	1111 (68)	592 (56)*
Hispanic	233 (13)	228 (26)*	271 (17)	286 (27)*
Race				
White	1311 (74)	540 (61)*	946 (58)	519 (50)*
Black	254 (14)	213 (24)*	289 (18)	266 (25)*
Other	201 (11)	132 (15)*	394 (24)	265 (25)*
COPD	109 (6.2)	76 (8.6)*	55 (3.4)	41 (3.9)
Cerebrovascular disease	22 (1.2)	7 (0.8)	44 (2.7)	66 (6.3)*
Previous MI (>24 h)	725 (41)	308 (35)*	379 (23)	211 (20)
CHF (within 2 weeks)	84 (4.8)	70 (7.9)*	54 (3.3)	56 (5.3)*
CHF (>2 weeks)	72 (4.1)	63 (7.1)*	37 (2.3)	41 (3.9)*
Priority				
Elective	856 (49)	401 (45)	924 (57)	630 (60)
Urgent	910 (52)	484 (55)	705 (43)	420 (40)
Creatinine (>2.5 mg/dL)	67 (3.8)	25 (2.8)	22 (1.4)	15 (1.4)
Renal dialysis	60 (3.4)	19 (2.1)	19 (1.2)	12 (1.1)
CCS class				
0	4 (0.2)	9 (1.0)*	18 (1.1)	16 (1.5)
1	43 (2.4)	11 (1.2)*	10 (0.6)	8 (0.8)
2	367 (21)	169 (19)	477 (29)	303 (30)
3/4	1352 (77)	696 (79)	1124 (69)	723 (69)

SD: standard deviation, BMI: body mass index, BSA: body surface area, COPD: chronic obstructive pulmonary disease, MI: myocardial infarction, CHF: congestive heart failure, CCS: Canadian cardiovascular society.

^a Patients: BMS (1998–2009) and DES (2003–2009).

* Indicates statistically significant *p*-value (*p* < 0.05).

were derived for both mortality and re-intervention outcomes at 1, 5 and 9 (or maximum) year follow-up for all multivessel patients and then repeated for two and three vessel patients separately. The DES1 versus DES2 mortality and re-intervention analyses were truncated at 4 and 3 years, respectively, based on available follow-up. In all instances, Cox regression analysis was used with comprehensive covariate adjustment for the following clinical and angiographic factors: age, gender, ejection fraction, procedure priority (elective or urgent), body surface area, body mass index category, previous MI, stroke, cerebrovascular accident, peripheral vascular disease, current or past congestive heart failure, chronic obstructive pulmonary disease, creatinine level, renal dialysis, left main trunk disease, and proximal left anterior descending artery disease. Diabetes, stent-type, and number of diseased vessels were additionally used as necessary in non-stratified analyses. The effect of DM versus NoDM was then estimated using propensity score regression adjustment, where a multivariate model with the mentioned clinical and angiographic covariates generated the propensity score estimate. The estimate was then included as a separate covariate in the above Cox regression model. Given the 1998–2009 study period, we also adjusted for stent-type era [1998–2002 (BMS only) versus 2003–09 (BMS/DES)] and for DES generation (first versus second). A two-sided *p*-value of 0.05 was adopted to indicate significance in all cases. Analyses were done using SPSS version 21.0 software (IBM, Armonk, NY, USA).

3. Results

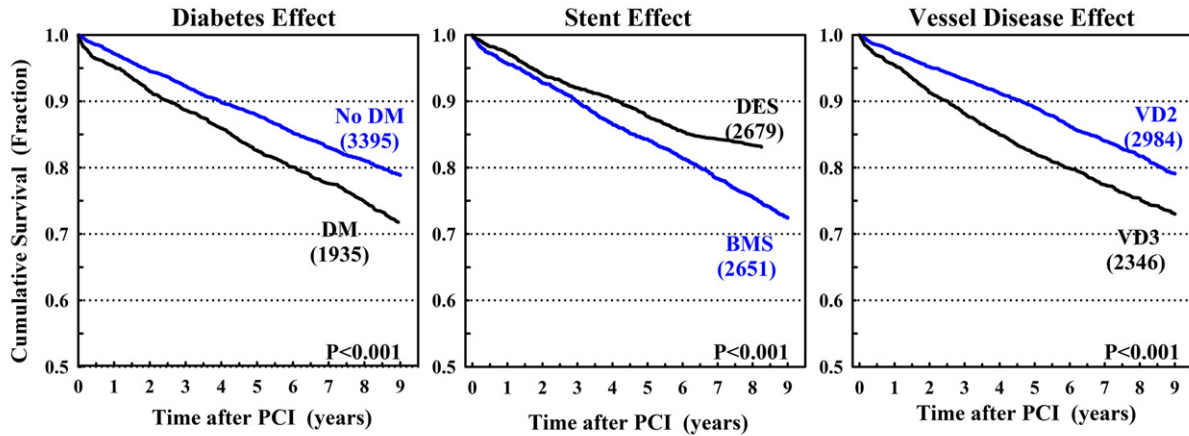
The overall study population consisted of 5330 unique multivessel CAD patients [3398 men (64%); 66.3 ± 11.7 years; 1935 diabetic (DM: 36%); 2346 three-vessel disease (44%)] undergoing a first PCI. Patients were about equally divided to groups of 2651 BMSPCI (50%) and 2679 DESPCI (50%). The frequency of 3-vessel disease patients increased

systematically over the 12-year study period from 29% in 1998 up to 54% in 2008–9 indicative of changing PCI practices in the United States. A similar increasing trend was observed in the proportion of DM to NoDM, where diabetic patients increased from 28.0% in 1998 up to about 42% in 2008–9. Paralleling this, diabetes was more frequent among DES (*n* = 1050; 39%) compared to BMS (*n* = 885; 33%) patients [*p* < 0.001]. An appreciable fraction of PCI patients were both diabetic and had 3-vessel disease (overall: *n* = 913; 17.1%) and this segment nearly doubled over the study period from 12% (1998–9) up to 23% (2008–9).

Compared to non-diabetic counterparts, diabetics were on average 1.1 years younger, relatively more female (DM vs. NoDM: 44% vs. 32%) and non-white (44% vs. 33%), had higher body mass index, and had more cerebrovascular and peripheral vascular disease (Table S-1; online supplement). Demographic and risk factor data for the DM and NoDM sub-cohorts are compared separately for BMS and DES treated patients in Table 1.

Table S-2 summarizes the separate comparisons of CAD characteristics and the first PCI details for DM versus NoDM patients within the BMS and DES treated groups. DES patients, irrespective of diabetes status, were more likely to have three-vessel disease (48% vs. 40%, *p* < 0.001) and have LAD disease (92% vs. 86%, *p* < 0.001) including significant proximal LAD lesions (44% vs. 39%, *p* < 0.001). For the BMS cohort, the CAD profiles were similar for the diabetic and non-diabetic subgroups. In contrast, for the DES cohort, 3-vessel disease was more frequent among the diabetic subgroup (53% vs. 44%; *p* < 0.001), while other CAD characteristics were similar. For the index procedure or first PCI, a larger number of stented lesions per patient were performed among DES (NoDM: 1.58 ± 0.67; DM: 1.53 ± 0.65) compared to BMS (NoDM: 1.37 ± 0.64; DM: 1.37 ± 0.62) treated patients (overall, *p* < 0.001) as is expected given their greater propensity for three-vessel disease. Overall, 48% of DES patients had multiple stented lesions

I. Survival



II. Re-intervention

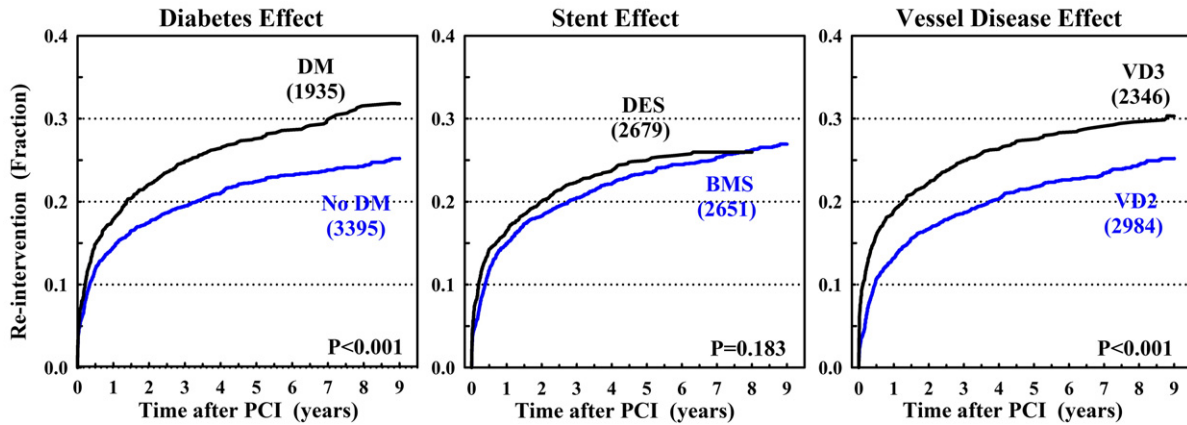


Fig. 2. Unadjusted 9-year Kaplan–Meier survival analysis comparing mortality (top) and re-intervention (bottom) for the overall DM versus NoDM groups (left), BMS versus DES groups (middle) and two-vessel versus three-vessel disease (right).

compared to only 30% in BMS counterparts ($p < 0.001$; Table S-2). LAD stenting (including proximal) was relatively more frequent in DES patients particularly in non-diabetics (20% vs. 15%). Very few patients have undergone complete revascularization (7.2%) with similar distribution among DM and NoDM patients within the BMS and DES treated groups.

The overall median (interquartile range) all-cause mortality and re-intervention follow-ups (truncated at 9 years) were 7.3 (4.9–9.0) and 3.8 (1.5–7.2) years, respectively. The corresponding follow-up was expectedly lower for DES [6.4 (4.5–8.0) and 2.8 (1.3–5.1)] versus BMS treated patients [9.0 (5.8–9.0) and 6.1 (1.9–9.0)]. Considering the overall study population, the 0-to-9 year survival was worse in diabetic

Table 2
Diabetes effect adjusted hazard ratios estimated for early, intermediate and late survival and re-intervention outcomes in BMS and DES treated patients.

	Counts	Early (1-year)		Intermediate (5-year)		Late (9-year ^a)		
		NoDM/DM (%)	AHR [95% CI]	NoDM/DM (%)	AHR [95% CI]	NoDM/DM (%)	AHR [95% CI]	
A. Mortality								
BMS	Multivessel	1766/885	3.1/6.9 [†]	2.51 [1.70–3.70]	13.2/20.9*	1.86 [1.52–2.28]	24.3/34.2*	1.71 [1.50–2.01]
	2-vessel	1055/524	2.2/5.0*	2.83 [1.51–5.32]	10.7/16.9*	1.80 [1.34–2.42]	21.6/30.9*	1.72 [1.39–2.14]
	3-vessel	711/361	4.4/9.7*	2.59 [1.54–4.36]	16.8/26.8*	2.01 [1.51–2.68]	28.3/38.9*	1.74 [1.37–2.21]
DES	Multivessel	1629/1050	2.5/3.0	1.45 [0.88–2.39]	10.9/13.2*	1.47 [1.61–1.87]	15.4/19.5*	1.41 [1.14–1.74]
	2-vessel	907/498	2.1/2.2	1.23 [0.56–2.72]	8.7/10.1	1.35 [0.91–2.01]	13.8/14.7	1.14 [0.81–1.61]
	3-vessel	722/552	3.1/3.6	1.79 [0.90–3.60]	14.2/18.3	1.64 [1.21–2.21]	17.1/24.0*	1.67 [1.26–2.22]
B. Re-intervention								
BMS	Multivessel	1766/885	13.7/17.4*	1.18 [0.96–1.46]	21.7/27.2*	1.22 [1.03–1.48]	24.6/31.9*	1.27 [1.08–1.50]
	2-vessel	1055/524	12.2/17.0*	1.29 [0.97–1.72]	20.4/26.5*	1.25 [0.99–1.57]	23.1/32.0*	1.33 [1.07–1.65]
	3-vessel	711/361	16.0/17.8	1.10 [0.79–1.53]	23.8/28.1	1.21 [0.92–1.59]	26.9/31.6	1.21 [0.93–1.58]
DES	Multivessel	1629/1050	15.3/18.2*	1.16 [0.95–1.41]	23.1/27.9*	1.16 [0.98–1.38]	24.0/29.2*	1.16 [0.98–1.37]
	2-vessel	907/498	11.7/14.2	1.21 [0.89–1.66]	19.4/23.9	1.20 [0.93–1.55]	20.6/25.3	1.19 [0.92–1.53]
	3-vessel	722/552	19.9/21.9	1.12 [0.87–1.44]	27.7/31.5	1.12 [0.90–1.40]	28.2/32.8	1.13 [0.90–1.41]

AHR: adjusted hazard ratio (bold indicates statistically significant). Corresponding unadjusted analysis is shown in Table S-3.

^a Re-intervention follow-up for DES is available up to 8 years only.

* Indicates statistically significant p-value.

versus non-diabetic patients ($p < 0.001$), in patients treated with BMS versus DES ($p < 0.001$), and in patients with 3-vessel versus 2-vessel disease ($p < 0.001$) (Fig. 2). During the available follow-up period, 2245 of the 5330 patients had at least one or more coronary re-interventions (42%) following their index PCI including: 996 (19%) were planned (staged) PCIs, and thus were not considered events, versus unplanned PCIs ($n = 1158$; 22%) or CABG ($n = 91$; 1.7%). The overall median (interquartile range) for the first re-intervention was 5.0 (0.9–18.4) months, and this was substantially earlier in case of DES versus BMS patients (median: 3.3 vs. 6.7 months; $p < 0.001$). Re-interventions were relatively more frequent in diabetics whether treated with BMS [DM vs. NoDM: 245 (25%) vs. 396 (22%), $p < 0.001$] or DES [DM vs. NoDM: 262 (25%) vs. 346 (21%), $p = 0.011$].

Time-to-event analysis between 0 and 9 years (Fig. 2) showed worse re-intervention rates in diabetic versus non-diabetic ($p < 0.001$) and 3-vessel versus 2-vessel disease ($p < 0.001$) patients. Notably, re-interventions were similar overall for BMS and DES recipients ($p = 0.183$).

3.1. Diabetes effect

The study population was divided into four sub-cohorts based on vessel disease [2,3,or] and stent type (BMS or DES) combinations. Nine-year unadjusted Kaplan–Meier survival and re-intervention trends were compared for diabetics versus non-diabetics within each sub-cohort. The observed early (1-year), intermediate (5-year) and late (9-year) mortality and re-intervention estimates (%) are summarized in Table 2, while corresponding unadjusted hazard ratios are provided in Table S-3 of online supplement. Briefly, in BMS patients, diabetes was associated with worse overall survival irrespective of vessel disease (Fig. 3(A, B); both $p < 0.001$), and the increased mortality was significant for early, intermediate and late follow-up. Alternatively, in DES, diabetics showed worse unadjusted survival only in case of 3-vessel disease ($p = 0.026$), and this became apparent in the intermediate to late term (Fig. 3(C, D)). Importantly, the latter when stratified to DES1 and DES2, only showed a significant diabetes effect in case of 3-vessel disease treated with DES1 (Fig. 3(C, D)). Re-interventions were generally more frequent in the diabetics versus non-diabetics for all comparisons, albeit to different extent and significance levels (Fig. 3(E–H)).

Comprehensively adjusted hazard ratios [AHR_{DM/NoDM}] for the diabetes effect, derived for 1, 5 and 9 year follow-up for mortality and re-intervention outcomes, are summarized in Table 2. Late term AHRs are also shown in forest plot format (Fig. 4). Briefly, in BMS patients, diabetes was associated with a substantial adverse mortality effect for all follow-up intervals. This diabetes effect was comparable in 2-vessel and 3-vessel disease, particularly for late 9-year mortality (2-vessel: AHR = 1.72 [1.39–2.14] and 3-vessel: 1.74 [1.37–2.21]). In DES patients, the adverse diabetes effect on overall 9-year mortality (Fig. 4) was significant for multivessel disease overall (AHR = 1.41 [1.14–1.74]), but was noticeably less than the effect observed in BMS and was predominantly a 3-vessel disease effect (3-vessel: AHR = 1.67 [1.26–2.22] versus 2-vessel: AHR = 1.14 [0.81–1.61]). The multivessel DES results were generally consistent for DES1 and DES2 (Table 3).

The corresponding array of risk-adjusted analyses for re-intervention also showed a diabetes adverse effect, irrespective of vessel disease, for both BMS and DES PCI, and at all follow-up intervals (Table 2). However, for multivessel disease, our results suggested a relatively reduced diabetes-related increase in re-interventions with DES (Table 2) and particularly in DES2 (Table 3).

The area under the receiver operating curve for the propensity score model had a value of 0.640 (95% CI 0.617 to 0.662, $p < 0.001$) for BMS and 0.639 (95% CI 0.618 to 0.661, $p < 0.001$) for DES treated patients. This resulted in relatively no change in diabetes effect adjusted hazard ratios estimated for early, intermediate and late survival and re-intervention outcomes (Table S-4).

3.2. Stent effect

A complementary analysis shown in the online supplement estimated the stent effect in the same study population based on sub-cohorts of vessel disease (2 or 3) and diabetes status (DM or NoDM) combinations (Tables S-5, S-6, S-7).

4. Discussion

The optimal coronary revascularization method is an intensely debated topic both for surgical and percutaneous approaches. This is particularly true in certain higher risk patient groups such as diabetic and multivessel coronary disease patients. Our retrospective analysis of a large real world PCI experience aimed to quantify the intermediate-to-late term effects of diabetes on mortality and on the need for repeat revascularization following initial PCI treatment in patients with multivessel CAD, and how this diabetes effect was modified by the transition to the DES platform.

The main study findings were: (1) PCI mortality was worse in diabetics versus non-diabetics, worse for BMS versus DES PCI, and worse for 3-vessel versus 2-vessel disease patients; (2) coronary re-intervention rates were worse in diabetics versus non-diabetics and in 3-vessel versus 2-vessel disease patients, but were mostly comparable for BMS and DES; (3) for BMS, the diabetes adverse effect on mortality was substantial and comparable in 2-vessel and 3-vessel disease patients; (4) for DES treated patients, the diabetes related increase in mortality was essentially eliminated in case of 2-vessel disease and reduced in case of 3-vessel disease but only for the early-term; and (5) diabetes was associated with an increase in coronary re-interventions irrespective of extent of vessel disease, but more so in BMS than DES treated patients. Altogether, these observations support the inference that diabetes is associated with worse 9-year adverse outcomes irrespective of stent type used, albeit this effect is mitigated to varying degrees with DES use depending on extent of vessel disease. This synthesis was corroborated by additional stent effect analyses. The latter indicated that, compared to BMS-PCI, use of DES was associated with superior 0-to-9 year mortality outcomes irrespective of diabetes status or extent of vessel disease and possibly more so in diabetic patients. The results of the DES versus BMS re-intervention analyses were equivocal.

Studies that examined the diabetes effect on PCI outcomes are numerous [4–14], but are restricted to early and intermediate mortality. DES use in diabetics has generally been associated with decreased need for repeat revascularization compared to BMS [6–9]. Yet, whether this reduction in repeat revascularization translates to improved late survival in diabetics with DES remains controversial [7,8,10].

In a meta-analysis of DES treated patients from 18 randomized trials, Kedhi et al. [12] reported a significantly higher 1-year mortality hazard ratio of 1.91 [1.32–2.78] for diabetes. Our single institution real-world registry analysis showed a lower diabetes 1-year hazard ratio of 1.45 [0.88–2.38] in DES patients that was not statistically significant possibly due to the relatively small number of death events during the first year after PCI in our series of non-emergency first revascularization patients. Kedhi et al. [12] also reported significantly higher diabetes-related one-year target lesion (1.50 [1.21–1.86]) and target vessel (1.54 [1.28–1.58]) revascularization rates which, although relatively greater, is in the same direction as our trend for increased one-year re-intervention hazard rates of 1.16 [0.95–1.41] in diabetics treated with DES (Table 2). The DES safety in diabetic patients was questioned by Spaulding et al. [10] in another meta-analysis where the authors reported worse 4-year mortality in diabetic patients treated with DES compared to BMS. This meta-analysis, however, was followed by other analyses with large sample sizes [9,13] that failed to show any important safety concerns associated with DES use in diabetics compared to BMS.

Long-term PCI mortality studies are relatively scarce, and are mostly available from larger studies that compared PCI of various modalities (mostly balloon angioplasty and BMS) to other revascularization

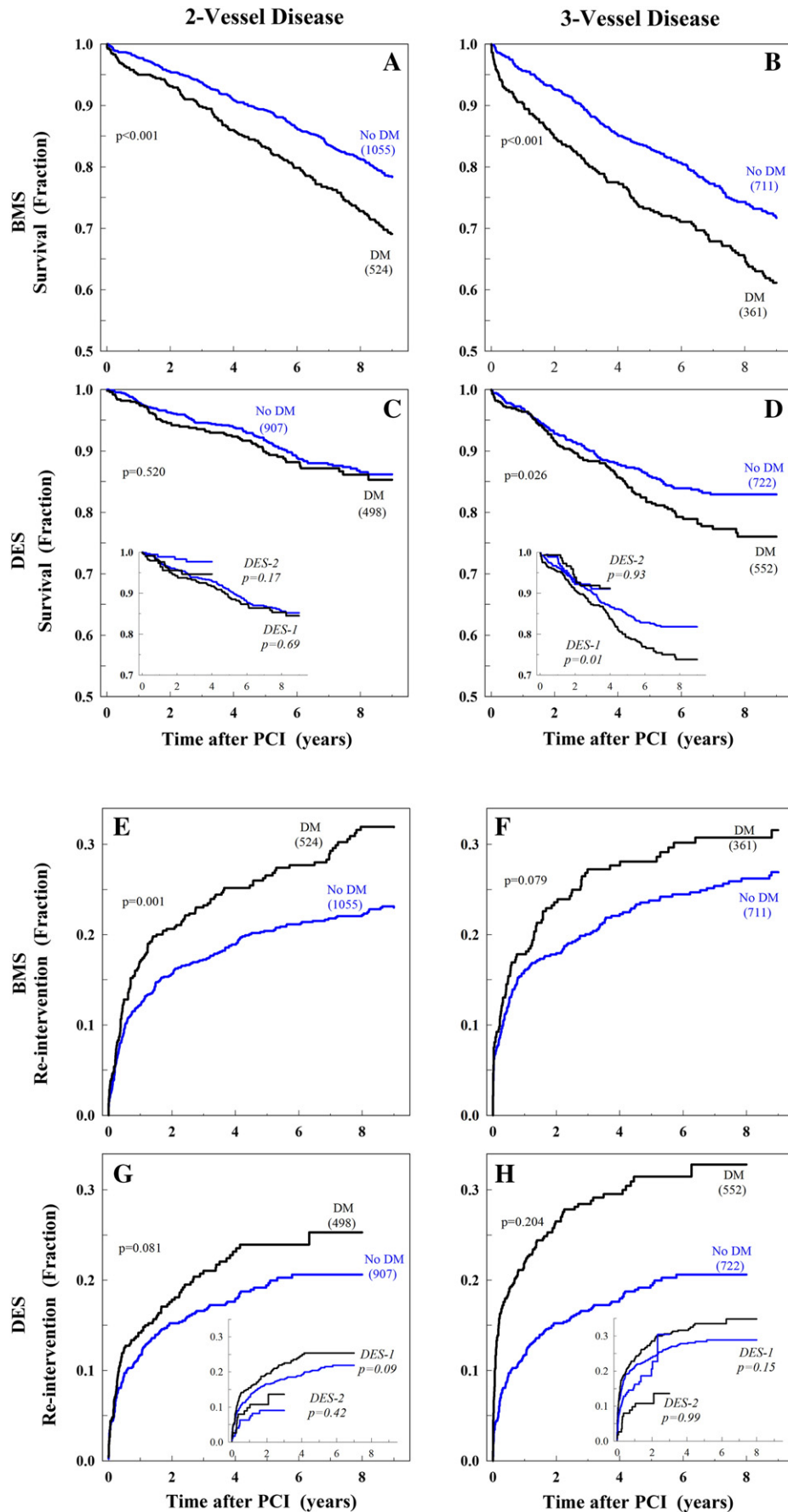
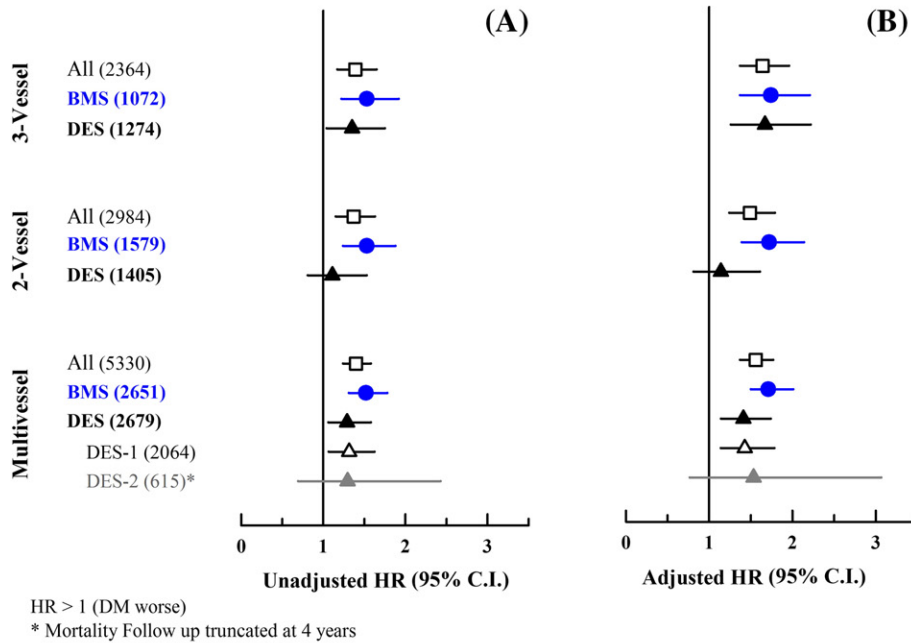


Fig. 3. Unadjusted 9-year Kaplan–Meier survival (A–D) and re-intervention (E–H) analysis separately comparing DM versus NoDM groups in BMS and DES treated patients. These results are shown stratified into their two-vessel (left) and three-vessel disease (right) subgroups.

Diabetes Effect (Late Mortality)



Diabetes Effect (Re-intervention)

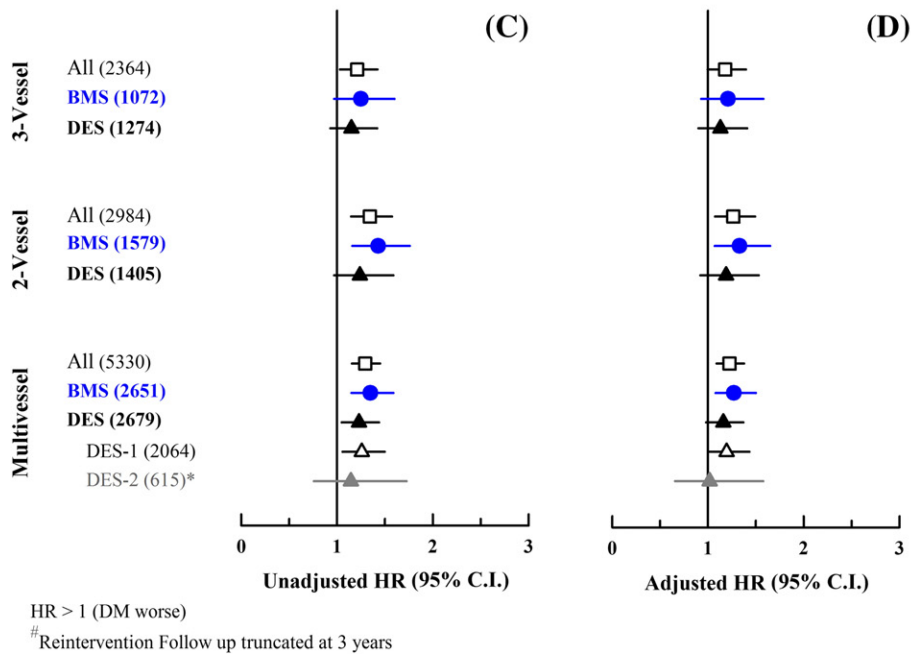


Fig. 4. Forest plot of 9-year “Diabetes Effect” or DM/NoDM unadjusted and risk-adjusted hazard ratios shown for all-cause mortality (panels A and B) and re-intervention (panels C and D) outcomes.

modalities (e.g., CABG and medical treatment). For example, Timmer et al. [15], in an observational data set, and the authors of the MASS II trial [16] suggest higher 10-year PCI mortality rates in diabetics. The longest mortality follow-up comparing DES versus BMS is reported in a sub-analysis of the SIRUS trial which compared SES (sirolimus) to BMS in symptomatic coronary disease [17]. Interestingly, they showed higher 5-year mortality in diabetics treated with SES (DM: 15.3% vs.

NoDM: 6.2%, $p < 0.01$) but not with BMS (DM: 9.5% vs. NoDM: 8.0%, $p = 0.60$). Yet, the authors cautioned that their results should be carefully interpreted given the small number of diabetic patients enrolled in their trial. In our observational study of PCI for multivessel CAD, five-year mortality rates were higher in diabetics regardless of stent type (BMS: 1.86 [1.52–2.28] and DES: 1.47 [1.21–2.21]) albeit with a lower mortality diabetes effect in DES patients.

Table 3
Diabetes effect adjusted hazard ratios estimated for survival and re-intervention outcomes in DES1 and DES2 treated.

		Counts	Late ^a	
		NoDM/DM	UHR [95% CI]	AHR [95% CI]
A. Mortality				
DES1	Multivessel	2064	1.31 [1.06–1.63]	1.43 [1.14–1.79]
	2-vessel	1118	1.07 [0.77–1.49]	1.08 [0.75–1.55]
	3-vessel	946	1.44 [1.08–1.9]	1.81 [1.34–2.45]
DES2	Multivessel	615	1.30 [0.69–2.43]	1.53 [0.77–3.07]
	2-vessel	287	2.37 [0.67–8.39]	3.14 [0.85–11.6]
	3-vessel	328	0.97 [0.47–2.01]	1.29 [0.55–3.04]
B. Re-intervention				
DES1	Multivessel	2064	1.26 [1.06–1.50]	1.20 [0.99–1.43]
	2-vessel	1118	1.25 [0.96–1.62]	1.21 [0.92–1.58]
	3-vessel	946	1.19 [0.94–1.51]	1.16 [0.91–1.49]
DES2	Multivessel	615	1.15 [0.76–1.73]	1.02 [0.66–1.58]
	2-vessel	287	1.36 [0.65–2.86]	1.17 [0.51–2.68]
	3-vessel	328	1.00 [0.61–1.64]	0.97 [0.57–1.66]

AHR: adjusted hazard ratio (bold indicates statistically significant).

^a Mortality follow-up for DES2 is only available up to 4 years. Re-intervention follow-up for DES1, DES2 are available up to 8 and 3 years respectively.

Hillegass and colleagues [14] compared long-term PCI outcomes in diabetic versus non-diabetic PCI patients for the elderly Medicare cohort of the National Cardiovascular Data Registry (2004–2008). Their 4-year mortality and 18-month re-intervention analyses did not sub-select multivessel disease, first revascularization and non-emergency PCIs. They report that (1) diabetes was associated with higher mortality and repeat re-intervention in both DES and BMS, and (2) the adverse 3-year diabetes effect on mortality was mitigated by the use of DES. Our results, with nearly three-times longer follow-up in patients from all age groups paralleled theirs. Hillegass et al. also showed decreased repeat revascularization in diabetics treated with DES, although less prominently than in randomized trials [14]. Our risk-adjusted 0-to-9 year revascularization analysis showed no reduction in re-intervention with DES (AHR = 1.00 [0.89–1.13]) and was similar in diabetics and non-diabetics (Fig. S-2(D)). However, when stratified by vessel disease, these outcome comparisons varied such that there was a trend for DES protection in case of two-vessel (AHR = 0.85 [0.72–1.01]) versus an opposite trend for increased re-intervention rates with DES in three-vessel (AHR = 1.16 [0.98–1.38]) disease.

Both the high rate of restenosis and the development of vulnerable plaques outside the stented segment, compromise long term PCI outcomes in diabetics [18]. Hence, when interpreting our re-intervention findings, it is crucial to note that they reflect a patient-based and not a stent or lesion based analysis. Accordingly, re-intervention could reflect revascularization of either the previously stented lesion or other new distinct lesion(s). A similar observation was reported in an analysis of a real-world registry by Yock et al. [19], where the reported repeat re-intervention was reduced with DES versus BMS for the stented segment, even if to a lesser extent than has been reported in randomized trials. This, however, was counterbalanced by an increase in re-intervention to treat remote segments in DES versus BMS. Accordingly, Yock and her colleagues reported an unchanged DES-to-BMS overall rate of one-year re-intervention. The expected benefit of DES PCI over BMS in regard to repeat interventions was not observed. This could be due to unaccounted bias that our analysis did not adjust for. However, if such bias does exist, it would similarly affect both our survival and re-intervention findings.

The authors of the multicenter, randomized Norwegian Coronary Stent Trial (NORSTENT) compared 6-year outcomes between CAD patients undergoing contemporary BMS versus DES [20]. They reported no significant difference in the rates of death from any cause or nonfatal spontaneous myocardial infarction between the two groups, but significantly lower rates of repeat revascularization in the group receiving DES [20]. The NORSTENT trial, however, consisted mostly of single

vessel CAD patients without diabetes, but its findings refute the common claim that there is no longer a role for bare-metal stents in PCI due to the presumed superiority of their drug-eluting counterparts.

5. Limitations

Our analysis has strengths as well as limitations. Strengths include the longer 9-year follow-up, the real world practice aspect from a high volume interventional center, and inclusion of all age groups. The present analysis shares inherent limitations of other observational retrospective studies. Our database did not differentiate diabetic patients into those requiring insulin or not and it did not account for diabetes progression. Information on antiplatelet use post-PCI is unavailable and may be relevant given the prothrombotic state and impaired response to dual antiplatelet therapy in diabetics. Similarly, information on concomitant utilization of disease modifying medications is unavailable and may be relevant given its known effect on survival.

We are unable to evaluate interventional complexity due to lack of data detailing specific lesion characteristics and we are unable to quantify the effect of change in PCI strategies during the long term follow-up of this study (1998–2009). The relatively smaller number of patients treated with second generation DES and their limited follow-up period did not allow for a meaningful stratified sub-analysis based on DES generation. To mitigate this, we included DES generation [1,2,or] as a covariate in our comprehensive risk-adjustment. Another potential limitation may be related to the potential risk of selection bias due to inclusion of patients who received BMS after the emergence of DES in 2003. Yet, for stent effect calculations, we (a) adjusted for stent era and (b) repeated the analyses excluding the minority of patients that received BMS-PCI after 2003. These mitigating measures resulted in essentially unchanged comparisons (Tables S-8 and S-9; online supplement).

6. Conclusion

In conclusion, this comprehensive and systematic analysis of a large real-world PCI series indicates that diabetes is associated with worse 9-year mortality irrespective of stent type, albeit this is mitigated to varying degrees with DES, particularly in DES2 and in case of 2-vessel disease. Complementary stent-effect analyses confirmed DES-to-BMS and DES2-to-DES1 superiority irrespective of vessel disease and in both diabetics and non-diabetics. The results of the DES versus BMS re-intervention analyses were equivocal.

Acknowledgments

We thank Dr. John Bittl, MD for reviewing the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.carrev.2017.01.012>.

References

- [1] Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabet Med J Br Diabet Assoc* 1997;14(Suppl. 5):S1–85.
- [2] Li Y, Woo V, Bose R. Platelet hyperactivity and abnormal Ca(2+) homeostasis in diabetes mellitus. *Am J Physiol Heart Circ Physiol* 2001;280(4):H1480–9.
- [3] Armstrong EJ, Rutledge JC, Rogers JH. Coronary artery revascularization in patients with diabetes mellitus. *Circulation* 2013;128(15):1675–85.
- [4] Mathew V, Gersh BJ, Williams BA, et al. Outcomes in patients with diabetes mellitus undergoing percutaneous coronary intervention in the current era: a report from the Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial. *Circulation* 2004;109(4):476–80.
- [5] Wilson SR, Vakili BA, Sherman W, Sanborn TA, Brown DL. Effect of diabetes on long-term mortality following contemporary percutaneous coronary intervention: analysis of 4,284 cases. *Diabetes Care* 2004;27(5):1137–42.
- [6] Caixeta A, Leon MB, Lansky AJ, et al. 5-Year clinical outcomes after sirolimus-eluting stent implantation insights from a patient-level pooled analysis of 4 randomized

- trials comparing sirolimus-eluting stents with bare-metal stents. *J Am Coll Cardiol* 2009;54(10):894–902.
- [7] Ortolani P, Balducelli M, Marzaroli P, et al. Two-year clinical outcomes with drug-eluting stents for diabetic patients with de novo coronary lesions: results from a real-world multicenter registry. *Circulation* 2008;117(7):923–30.
- [8] Ramanath VS, Brown JR, Malenka DJ, et al. Outcomes of diabetics receiving bare-metal stents versus drug-eluting stents. *Catheter Cardiovasc Interv* 2010;76(4):473–81.
- [9] 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.
- [10] Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;356(10):989–97.
- [11] 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(4):357–68.
- [12] 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(20):2111–8.
- [13] Bangalore S, Kumar S, Fusaro M, et al. Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22,844 patient years of follow-up from randomised trials. *BMJ* 2012;345:e5170.
- [14] Hillegass WB, Patel MR, Klein LW, et al. Long-term outcomes of older diabetic patients after percutaneous coronary stenting in the United States: a report from the National Cardiovascular Data Registry, 2004 to 2008. *J Am Coll Cardiol* 2012;60(22):2280–9.
- [15] Timmer JR, Breeman A, Ottervanger JP, de Kluiver EP, Boonstra PW, Zijlstra F. Long-term clinical outcome of patients with diabetes proposed for coronary revascularisation. *Neth J Med* 2006;64(8):296–301.
- [16] Lima EG, Hueb W, Garcia RMR, et al. Impact of diabetes on 10-year outcomes of patients with multivessel coronary artery disease in the Medicine, Angioplasty, or Surgery Study II (MASS II) trial. *Am Heart J* 2013;166(2):250–7.
- [17] Weisz G, Leon MB, Holmes DR, et al. Five-year follow-up after sirolimus-eluting stent implantation results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial. *J Am Coll Cardiol* 2009;53(17):1488–97.
- [18] Bittl JA. Percutaneous coronary interventions in the diabetic patient: where do we stand? *Circ Cardiovasc Interv* 2015;8(4):e001944.
- [19] Yock CA, Isbill JM, King SB, Hlatky MA. Repeat coronary revascularization procedures after successful bare-metal or drug-eluting stent implantation. *J Invasive Cardiol* 2010;22(1):27–33.
- [20] Bønaa KH, Mannsverk J, Wiseth R, et al. Drug-eluting or bare-metal stents for coronary artery disease. *N Engl J Med* 2016;375(13):1242–52.