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Original Article

Clinical Outcome of Diabetic Patients Treated by Percutaneous Coronary Intervention Using Drug-Eluting and Bare Metal Stents

Edgar Stroppa Lamas[1], Antonio de Castro Filho[2], Marinella Patrizia Centemero[3], Henrique Chigueo Iwace[4], Fausto Feres[5], Rodolfo Staico[6], Dimytri Siqueira[7], J. Ribamar Costa Jr.[8], Ricardo Costa[9], Daniel Chamié[10], Áurea J. Chaves[11], Amanda G. M. R. Sousa[12], Alexandre Abizaid[13]

ABSTRACT

Background: Percutaneous revascularization in diabetic is frequent and the use of drug-eluting stents (DES) is desirable, since they reduce restenosis and the need for repeat revascularization. The objective of this study was to compare the long-term outcomes of diabetic patients treated with and without DES. **Methods:** A consecutive cohort of diabetic patients undergoing percutaneous coronary intervention (PCI) between January 2009 and December 2012 in a public tertiary hospital was prospectively followed-up. **Results:** Nine hundred and thirty-nine diabetic patients (38.3%) treated with DES and 580 (61.7%) treated with bare metal stents (BMS) were evaluated. The rate of major adverse cardiac events (MACE) in 12.6 ± 3.4 months was greater in the BMS group (9.5% vs. 14.8%; RR, 1.56; 95% CI, 1.07-2.27; P = 0.02), as well as death (2.8% vs. 6.7%; RR, 2.41; 95% CI, 1.22-4.77; P < 0.01), and target vessel revascularization (3.9% vs. 7.2%; RR, 1.85; 95% CI, 1.03-3.35; P = 0.04). There were no differences in the incidence of myocardial infarction (1.7% vs. 0.5%; RR, 0.30; 95% CI, 0.07-1.23; P = 0.08) or stroke (1.1% vs. 0.2%; RR, 0.15; 95% CI, 0.01-1.37; P = 0.07). Multivariate analysis indicated that chronic kidney disease (RR, 2.05; 95% CI, 1.40-2.98; P < 0.01) and acute coronary syndrome (RR, 2.08; 95% CI 1.42-3.02; P < 0.01) were the only independent predictors of MACE. **Conclusions:** In non-selected diabetic patients the long-term clinical outcome was worse for patients treated

RESUMO

Evolução Clínica de Pacientes Diabéticos Tratados por Intervenção Coronária Percutânea Utilizando Stents Com e Sem Eluição de Fármacos

Introdução: A revascularização percutânea de diabéticos é frequente e a utilização de stents farmacológicos (SF) é desejável, pois estes reduzem a reestenose e a necessidade de nova revascularização. O objetivo desse estudo foi comparar os resultados clínicos de longo prazo entre diabéticos tratados com e sem SF. **Métodos:** Analisou-se uma coorte consecutiva de diabéticos submetidos à intervenção coronária percutânea (ICP) entre janeiro de 2009 e dezembro de 2012, em hospital terciário da rede pública. Esses pacientes foram acompanhados prospectivamente. **Resultados:** Avaliamos 939 diabéticos, sendo 359 (38,3%) tratados com SF e 580 (61,7%) tratados com stents não farmacológicos (SNF). A taxa de eventos cardiovasculares adversos maiores (ECAM) em 12,6 ± 3,4 meses foi maior no grupo SNF (9,5% vs. 14,8%; risco relativo – RR = 1,56; intervalo de confiança de 95% – IC 95% 1,07-2,27; P = 0,02), assim como o óbito (2,8% vs. 6,7%; RR = 2,41; IC 95% 1,22-4,77; P < 0,01) e a revascularização do vaso alvo (3,9% vs. 7,2%; RR = 1,85; IC 95% 1,03-3,35; P = 0,04). Não foram observadas diferenças na incidência de infarto do miocárdio (1,7% vs. 0,5%; RR = 0,30; IC 95% 0,07-1,23; P = 0,08) ou acidente vascular encefálico (1,1% vs. 0,2%; RR = 0,15; IC 95% 0,01-1,37; P = 0,07). A análise multivariada revelou que a

[1] Resident Physician at the Department of Invasive Cardiology of Instituto Dante Pazzanese de Cardiologia. São Paulo, SP, Brazil.
[2] Resident Physician at the Department of Invasive Cardiology of Instituto Dante Pazzanese de Cardiologia. São Paulo, SP, Brazil.
[3] Doctor. Cardiologist at the Department of Invasive Cardiology of Instituto Dante Pazzanese de Cardiologia. São Paulo, SP, Brazil.
[4] Resident Physician of Cardiology of Instituto Dante Pazzanese de Cardiologia. São Paulo, SP, Brazil.
[5] Doctor. Interventionist Cardiologist at the Department of Invasive Cardiology of Instituto Dante Pazzanese de Cardiologia. São Paulo, SP, Brazil.
[6] Doctor. Interventionist Cardiologist at the Department of Invasive Cardiology of Instituto Dante Pazzanese de Cardiologia. São Paulo, SP, Brazil.
[7] Doctor. Interventionist Cardiologist at the Department of Invasive Cardiology of Instituto Dante Pazzanese de Cardiologia. São Paulo, SP, Brazil.
[8] Doctor. Interventionist Cardiologist at the Department of Invasive Cardiology of Instituto Dante Pazzanese de Cardiologia. São Paulo, SP, Brazil.
[9] Doctor. Interventionist Cardiologist at the Department of Invasive Cardiology of Instituto Dante Pazzanese de Cardiologia. São Paulo, SP, Brazil.
[10] Interventionist Cardiologist, Department of Invasive Cardiology, Instituto Dante Pazzanese de Cardiologia. São Paulo, SP, Brazil.
[11] Doctor. Cardiologist, Department of Invasive Cardiology, Instituto Dante Pazzanese de Cardiologia. São Paulo, SP, Brazil.
[12] Full-Professor. General Director, Instituto Dante Pazzanese de Cardiologia. São Paulo, SP, Brazil.
[13] Full-Professor. Director, Division of Invasive Cardiology, Instituto Dante Pazzanese de Cardiologia. São Paulo, SP, Brazil.

Correspondence: Marinella Patrizia Centemero. Serviço de Cardiologia Invasiva do Instituto Dante Pazzanese de Cardiologia. Avenida Dante Pazzanese, 500 – Vila Mariana – São Paulo, SP, Brazil – CEP 04012-180
E-mail: mpcentemero@yahoo.com.br

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with BMS. After adjusting for confounding variables, the use of DES was not an independent predictor of reduced MACE.

DESCRIPTORS: Percutaneous coronary intervention. *Diabetes mellitus*. Drug-eluting stents. Coronary artery disease.

doença renal crônica (RR = 2,05; IC 95% 1,40-2,98; P < 0,01) e a síndrome coronária aguda (RR = 2,08; IC 95% 1,42-3,02; P < 0,01) foram os únicos preditores independentes de ECAM. **Conclusões:** Em pacientes diabéticos não selecionados, a evolução clínica tardia foi pior para os tratados com SNF. Após o ajuste das variáveis de confusão, o uso de SF não se mostrou preditor independente da redução de ECAM.

Descritores: Intervenção coronária percutânea. *Diabetes mellitus*. Stents farmacológicos. Doença da artéria coronariana.

Coronary artery disease (CAD) accounts for approximately 75% of cardiovascular deaths in diabetics.[1] A considerable number of these patients undergo percutaneous coronary intervention (PCI), whether in the presence of acute conditions or for the treatment of the stable disease; currently, diabetics represent approximately 30% of those percutaneously revascularized patients.[2]

In these patients, CAD has peculiar characteristics, either due to the association of comorbidities, which increase the clinical risk, or to the presence of more extensive and complex atherosclerotic disease, with smaller vessels and a greater propensity to thrombosis. Specifically regarding PCI, this subgroup has a greater tendency to coronary restenosis after stent implantation, and a higher incidence of other adverse cardiac events in the late evolution, such as death and acute myocardial infarction (AMI).[3-5]

In turn, drug-eluting stents (DES) have proven their effectiveness in reducing restenosis and the need for additional revascularization procedures when compared to bare metal stents (BMS) in both the overall population and in the diabetic subgroup.[6,7] In these latter patients, drug-eluting prostheses have also been widely investigated, demonstrating high success rates, low rates of acute complications, and significant reduction of new revascularizations when compared to BMS.[8]

However, the results related to major cardiovascular safety outcomes, such as death, AMI, and stroke in the medium- to long-term are still contradictory.[7-9] Some international registries have observed reduction of mortality and AMI in favor of DES in diabetic patients, in both early and late stages[10] – benefits not observed in other series.[11,12] More recent randomized trials comparing these prostheses with CABG in multivessel diabetics also failed to demonstrate favorable results for DES.[13,14]

In Brazil, where the majority of CAD patients are treated in the public health network, subject to curtailment of funds provided by the Brazilian Unified Health System (Sistema Único de Saúde – SUS), the acquisition of DES for universal use is impractical. In this context, the availability of these devices, with a much higher cost than that of BMS, could occur in the treatment of subgroups with more complex coronary anatomy, such as diabetics.

Thus, this study aimed to investigate the late clinical outcome in diabetic patients treated with PCI, with and without DES implantation.

METHODS

From January 2009 to December 2011, a consecutive cohort of diabetic patients undergoing PCI in the Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil, a tertiary public hospital with extensive experience in percutaneous procedures, was analyzed.

The primary objective was to compare the rate of major adverse cardiovascular events (MACE), defined as death, stroke, AMI, and target vessel revascularization (TVR) in diabetic patients treated with and without DES. The secondary objective was to evaluate the rates of occurrence of each clinical event isolated in both groups, as well as to identify possible independent predictors of MACE.

Definitions

Diabetes mellitus was diagnosed according to the criteria of the American Diabetes Association: presence of fasting glucose values ≥ 126 mg/dL, or glycated hemoglobin ≥ 6.5%, or glucose ≥ 200 mg two hours after a glucose overload. Death was defined as any death, regardless of cause, and cardiac death as a death secondary to immediate cardiac causes (AMI, heart failure, and fatal arrhythmia), in addition to unwitnessed deaths and/or deaths due to unknown causes.

The diagnosis of AMI was established when periprocedural elevation of CK-MB > 3 times the upper limit of normal was observed, in association with symptoms indicative of myocardial ischemia or with the presence of new Q waves on ECG after the procedure, or with changes in regional contractility on imaging exams during the in-hospital stay. Conversely, the occurrence of AMI after discharge was considered in cases of a rise and fall of troponin or CK-MB levels, in association

with typical ischemic symptoms or with electrocardiographic changes (new Q waves/ST segment elevation or lowering), or with a need for urgent revascularization, or finally, in face of anatomopathological findings consistent with acute ischemia.

Stroke was defined as the occurrence of cerebral infarction (ischemic stroke) or subarachnoid and brain hemorrhage (hemorrhagic stroke), with symptoms persisting > 24 hours or that resulted in death < 24 hours.

TVR was defined as the performance of a new percutaneous or surgical procedure after discharge to treat the target vessel, in the presence of angina or of a clinical equivalent of ischemia, or in the presence of functional tests with abnormal results.

Stent thrombosis was defined according to the criteria of the Academic Research Consortium (ARC) as definite if confirmed by angiographic (Trombolysis in Myocardial Infarction [TIMI] flow = 0 with stent occlusion by thrombus or TIMI flow 1, 2, or 3 and presence of thrombus) or anatomopathological findings; or as probable, defined as any unexplained death within the first 30 days after PCI or any AMI related to the target vessel without angiographic confirmation and in the absence of any other causes.[15]

Procedure

The percutaneous procedure was performed according to the standard practice recommended by national and international guidelines.[16,17] The choice of access route (femoral or radial) was at the discretion of the surgeon, as well as the use of glycoprotein IIb/IIIa.

Dual antiplatelet therapy consisted of acetylsalicylic acid at a dose of 100 mg/day in patients with chronic use, and 300 mg (loading dose) in previously untreated patients. Clopidogrel was the P2Y12 inhibitor most frequently used, at loading doses of 300 to 600 mg before the procedure and, subsequently, 75 mg/day combined with acetylsalicylic acid 100 mg/day for one year.

The decision to use DES was at the surgeon's discretion and subject to the availability of the device at the time of the trial, considering the following scenarios: vessels ≤ 2.5 mm, lesions > 20 mm and in-stent restenosis; expectation of non-adherence to dual antiplatelet therapy at one year; presence of hemorrhagic diathesis, or of hematologic diseases, or prior and recent history (< six months) of digestive, urological, or other bleeding that could prevent the use of dual antiplatelet therapy for the recommended time.

Clinical follow-up

The clinical follow-up was prospective, and conducted by clinical visits with review of records, since this tertiary hospital has an outpatient setting for monitoring patients undergoing PCI. Contacts by phone, email, telegram, or reports from physicians who referred patients to this service were used.

Statistical analysis

Continuous variables were analyzed as means ± standard deviations and compared using the Mann-Whitney test. Categorical variables were compared using the chi-squared or Fisher's exact test, when appropriate.

Analysis of survival free of event was obtained using Kaplan-Meier curves, and comparisons were performed using the log-rank method.

Multivariate regression models were derived from Cox for MACE, and the variables considered for inclusion in the multivariate models were age, gender, insulin use, chronic renal failure (CRF), acute coronary syndrome (ACS), prior PCI, number of vessels treated, use of periprocedural DES, and AMI. The significance level for permanence in the model was adjusted to 0.01.

To perform the analysis, the SPSS, version 20.0, was used. P-values < 0.05 were considered significant.

RESULTS

939 consecutive diabetic patients were analyzed; 359 patients (38.3%) were treated with DES and 580 patients (61.7%) with BMS. Mean follow-up in both groups was 12.9 ± 3.6 months (1-13 months) and 12.4 ± 2.5 months (1-14 months), respectively, and 80% of patients had a minimum follow-up of one year.

Demographic and clinical characteristics of these patients revealed a higher proportion of patients with risk factors for atherosclerosis, previous AMI, heart failure, previous PCI, and stable clinical status in diabetic patients treated with DES, whereas patients with chronic kidney disease and ACS were more frequent in the group treated with BMS. Regarding the pharmacological treatment before the procedure, patients treated with DES most often used beta-blockers, statins, and insulin (Table 1).

In the DES group, the left anterior descending artery was the most frequently target vessel (50.7%), and multivessel PCI was more frequent (25.3% vs. 5.7%; P < 0.01), resulting in a ratio target vessel per patient/stent per patient also significantly higher in this group. A significantly higher percentage of bifurcation injuries and restenotic lesions was observed in patients treated with DES (Table 2). Zotarolimus- (65%), sirolimus- (31%), paclitaxel- (2.5%), and novolimus (1.5%) -eluting stents were used.

In relation to in-hospital outcomes, the clinical success rate of PCI was similar in both groups (97.2% vs. 95.6%; P = 0.22), with no differences in the occurrence of death (0% vs. 0.7%; P = 0.30) and stroke (0% vs. 0.2; P = 0.99). The group of patients treated with DES showed a higher incidence of elevation of

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TABLE 1
Clinical and demographic characteristics of patients

Characteristics	DES (n = 359)	BMS (n = 580)	P-value
Age, years	63.0 ± 10.6	63.2 ± 10.5	0.80
Female, n (%)	145 (40.4)	219 (37.8)	0.42
Hypertension, n (%)	337 (93.9)	533 (91.9)	0.30
Dyslipidemia, n (%)	314 (87.5)	453 (78.1)	< 0.01
Smoking, n (%)	204 (56.8)	62 (10.7)	< 0.01
Prior PCI, n (%)	104 (29.0)	64 (11.0)	< 0.01
Previous CABG, n (%)	35 (9.7)	88(11.0)	0.17
Prior AMI, n (%)	163 (45.4)	224 (38.6)	0.04
Prior stroke or TIA, n (%)	13 (3.6)	18 (3.1)	0.70
Family history of CAD, n (%)	73 (20.3)	52 (9.0)	< 0.01
COPD, n (%)	4 (1.1)	10 (1.7)	0.58
CRF not requiring dialysis, n (%)	27 (7.5)	188 (32.4)	< 0.01
POAD, n (%)	16 (4.5)	16 (2.8)	0.19
Heart failure, n (%)	127 (35.4)	9 (1.6)	< 0.01
Clinical status, n (%)			< 0.01
Acute coronary syndrome	36 (10.0)	174 (30.0)	
Stable angina	218 (60.7)	268 (46.2)	
Asymptomatic	105 (29.2)	138 (23.8)	
Pharmacological treatment, n (%)			
Insulin	106 (29.5)	58 (10.0)	< 0.01
Oral hypoglycaemic	313 (87.2)	520 (89.7)	0.24
Acetylsalicylic acid	357 (99.4)	568 (97.9)	0.09
Statins	357 (99.4)	537 (92.4)	< 0.01
ACEI/BRA	336 (93.6)	536 (92.4)	0.51
Beta blockers	343 (95.5)	477 (80.5)	< 0.01

DES = drug-eluting stents; BMS = bare metal stents; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft surgery; AMI = acute myocardial infarction; TIA = transient ischemic attack; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; POAD = peripheral obstructive arterial disease; ACEI/ARB = angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers.

periprocedural myocardial injury markers when compared to those treated with BMS (8.6% vs. 4.0%; P < 0.01).

In a clinical follow-up of 12.6 ± 3.4 months, the rate of MACE was higher in the group receiving BMS (9.5% vs. 14.8%; RR = 1.56; 95% CI: 1.07-2.27; P = 0.01). Death by the end of clinical follow-up was also higher in the BMS group (2.8% vs. 6.7%; RR = 2.41; 95% CI: 1.22-4.77; P < 0.01), as well as death of cardiac origin (1.7% vs. 3.7%; RR = 2.78; 95% CI: 1.16-6.68; P = 0.01) and TVR (3.9% vs. 7.2%; RR = 1.85; 95% CI: 1.03-3.35; P = 0.03). Moreover, there

TABLE 2
Angiographic and procedural characteristics

Characteristics	DES (n = 359)	BMS (n = 580)	P-value
Target vessels, n (%)			< 0.01
Left anterior descending artery	182 (50.7)	186 (32.1)	
Left circumflex artery	64 (17.8)	103 (17.7)	
Right coronary artery	61 (17)	200 (34.5)	
Left main coronary artery	1 (0.3)	9 (1.6)	
Saphenous graft, n (%)	14 (3.9)	37 (6.4)	0.10
Bifurcation, n (%)	79 (22)	57 (9.8)	< 0.01
Total occlusion, n (%)	10 (2.7)	17 (2.9)	0.89
Restenosis, n (%)	61 (17)	15 (2.6)	< 0.01
Number of vessels treated per patient	1.5 ± 0.22	1.0 ± 0.50	< 0.01
Treatment of two or more vessels, n (%)	91 (25.3)	33 (5.7)	< 0.01
Number of stents per patient	1.48 ± 0.5	1.07 ± 0.4	< 0.01
Stent caliber, mm	2.90 ± 4.2	3.10 ± 4.3	0.11
Stent length, mm	19.6 ± 9.3	20.5 ± 6.6	0.09

DES = drug-eluting stents; BMS = bare metal stents.

were no significant differences between the two groups in the incidence of AMI (1.7% vs. 0.5%; RR = 0.30; 95% CI: 0.07-1.23; P = 0.07) and stroke (1.1% vs. 0.2%; RR = 0.15; 95% CI: 0.01-1.37; P = 0.07) in the same trial period (Table 3).

The results of the Kaplan Meier curves regarding survival free of MACE, death, death of cardiac origin, and TVR are detailed in Figure 1, revealing significant differences in favor of DES.

In relation to definite or probable stent thrombosis, this complication had a very low incidence in both groups (0.83% vs. 0%; P = 0.06) during the relatively short follow-up period.

A multivariate analysis of pre-specified variables identified only chronic renal disease (CRD) (RR = 2.05; 95% CI: 1.40-2.98; P < 0.01) and ACS (RR = 2.08; 95% CI: 1.42-3.02; P < 0.01) as independent predictors for occurrence of MACE in the late evolution of diabetes (Table 4). The use of DES was shown to be a predictor of MACE in this group (RR = 1.35; 95% CI: 0.87-2.10; P = 0.17).

DISCUSSION

In the present study, which included a cohort of untreated, non-selected diabetic patients for PCI in a tertiary public hospital, a reduction of MACE, death, death due to a cardiac cause, and TVR in the group

TABLE 3
Cardiovascular events at the end of one year

Event	DES (n = 359)	BMS (n = 580)	RR	95% CI	P-value
MACE, n (%)	34 (9.5)	86 (14.8)	1.56	1.07-2.27	0.01
Death, n (%)	10 (2.8)	39 (6.7)	2.41	1.22-4.77	< 0.01
Cardiac death, n (%)	6 (1.7)	27 (3.7)	2.78	1.16-6.68	0.01
Stroke, n (%)	4 (1.1)	1 (0.2)	0.15	0.01-1.37	0.07
AMI, n (%)	6 (1.7)	3 (0.5)	0.3	0.07-1.23	0.07
TVR, n (%)	14 (3.9)	42 (7.2)	1.85	1.03-3.35	0.03

DES = drug-eluting stents; BMS = bare metal stents; RR = relative risk; 95% CI = 95% confidence interval; MACE = main adverse cardiovascular events; AMI = acute myocardial infarction; TVR = target vessel revascularization.

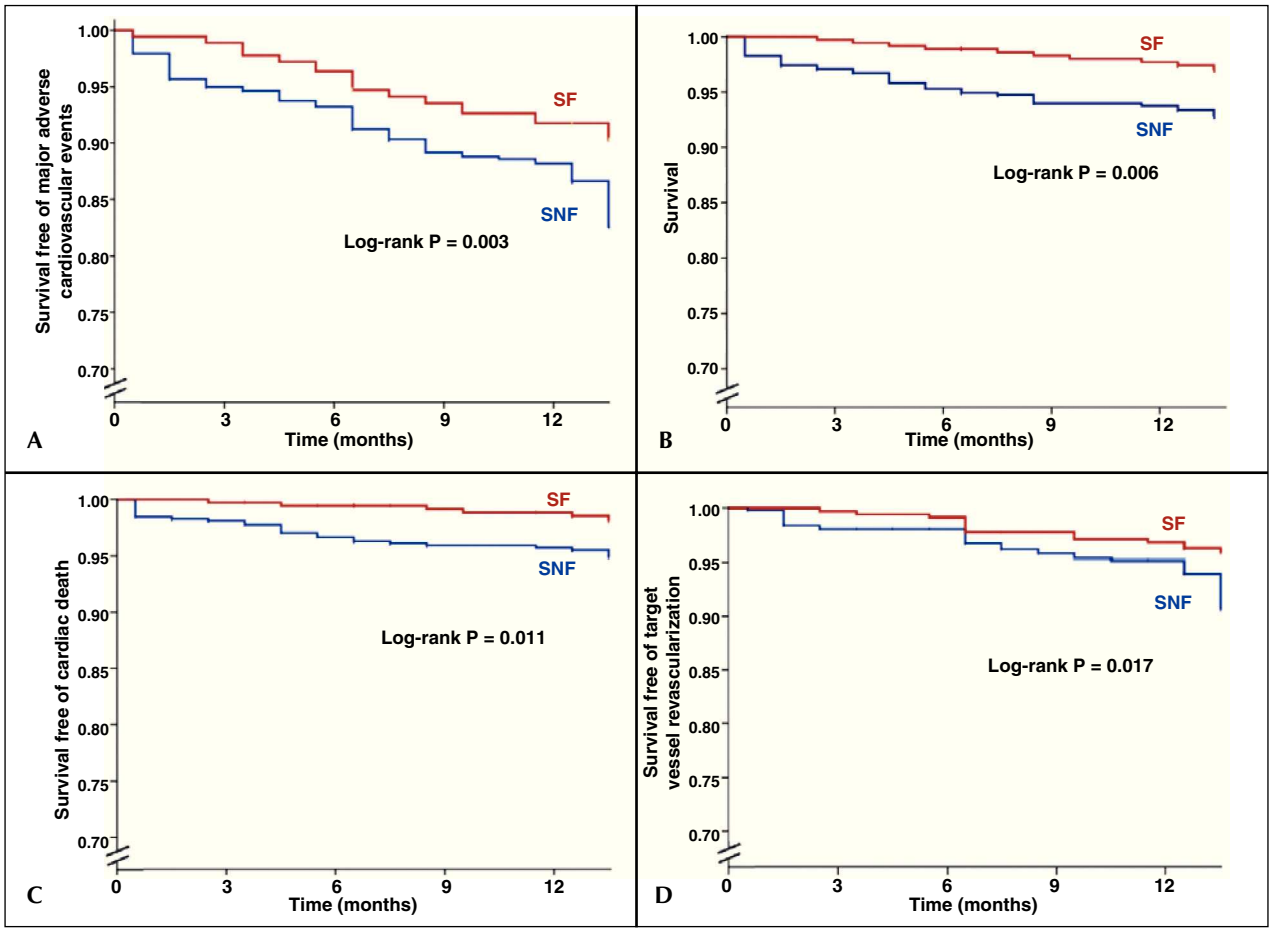

Figure – Curves: survival free of major adverse cardiovascular events (A); survival (B); survival free of cardiac death (C); survival free from target vessel revascularization (D). DES = drug-eluting stent; BMS = bare metal stent.

treated with DES was observed. However, after adjusting for confounding variables, the use of DES did not modify the occurrence of combined adverse events. Chronic renal disease and ACS were the only prespecified variables predictors of poorer clinical outcome.

Currently, the technological development of materials available for the completion of PCI, together with the vast experience of the surgeons in the management of high-risk patients and the availability of DES, allowed for the expansion of indications for percutaneous

TABLE 4
Predictors of major adverse cardiovascular events in diabetic patients

	RR	95% CI	P-value
Age	1.10	0.99-1.03	0.08
Gender	1.00	0.69-1.45	0.97
Insulin use	0.96	0.60-1.54	0.87
Chronic renal failure	2.05	1.40-2.98	< 0.01
Acute coronary syndrome	2.08	1.42-3.02	< 0.01
Previous PCI	0.80	0.48-1.33	0.40
Number of vessels treated	0.74	0.44-1.25	0.27
Heart failure	0.61	0.32-1.13	0.11
DES use	1.35	0.87-2.10	0.17
Periprocedural AMI	1.50	0.80-2.92	0.19

RR = relative risk; 95% CI = 95% confidence interval; PCI = percutaneous coronary intervention; DES = drug-eluting stent; AMI = acute myocardial infarction.

treatment, including patients with CAD of high clinical and anatomical complexity, such as diabetics.[16,17]

In the present study, it was observed that diabetics treated with DES corroborate this scenario, in that these patients presented more challenging angiographic characteristics, often involving the treatment of left anterior descending artery (with a greater area of myocardium at risk for ischemia), lesions located in bifurcations, and coronary restenoses. Acknowledging the complexity of the lesions treated, a greater number of vessels was approached, resulting in a significantly higher ratio of vessels treated per number of stents in the group of diabetics revascularized with DES. Such features require the use of more efficient prostheses, with elution of drugs that effectively inhibit neointimal proliferation, in order to reduce the recurrence of obstructions due to coronary restenosis, and, hence, the need for new revascularizations in patients already predisposed to these events.

In the literature, several trials comparing the use of DES vs. BMS in diabetic and nondiabetic patients have clearly demonstrated the superiority of the former device in significantly reducing coronary restenosis and, therefore, in a new approach to recurrent lesions, reducing the exposure of patients to the inherent risks of a new procedure, whether percutaneous or surgical.[7,11,12]

It is also interesting to note, in the present population, the greater proportion of patients using insulin in the DES group (29.5% vs. 10.0%; P < 0.01), indicating a greater severity and duration of diabetes. It is known that, in general, these patients may experience a more diffuse atherosclerotic disease and an intense inflammatory process of the coronary arteries and vascular beds in general, which result in greater predisposition to restenosis, arterial thrombosis, and AMI.[18-20] A recent brazilian publication[21] investigated in-hospital outcomes of nearly 2,000 diabetic patients from the Angiocardio Registry undergoing PCI, divided among those treated with insulin (21%) and those using oral hypoglycemic agents. The researchers found that, despite the higher percentage of women and of chronic kidney disease in the insulin subgroup, the major cardiovascular outcomes were similar in both groups, and the insulin treatment was not an independent predictor for the occurrence of adverse events in the in-hospital phase.

A register held by the National Heart, Lung, and Blood Institute in 2008, involving over 2,500 diabetic patients with and without insulin use treated with DES and BMS, revealed that the use of DES reduced the risk of repeat revascularization and of safety outcomes such as death and AMI. However, the reduction in mortality and in AMI was restricted to diabetics not treated with insulin.[21] It is noteworthy that, in the present study, the use of insulin was not a predictor of adverse cardiovascular events in the long-term.

Regarding in-hospital results, the present findings demonstrated equivalent procedural success rates between the two types of stents, as well as the rates of occurrence of death and stroke, confirming the safety and efficacy of DES in the earliest phase after PCI. The higher incidence of elevated markers of peri-PCI myocardial injury probably relates to the greater anatomical complexity of the lesions treated in the DES subgroup, with a larger number of approached vessels and of implanted stents.

Regarding stent thrombosis (definite or probable, according to ARC criteria), this occurrence was very low in both groups (0.83% vs. 0%) in a follow-up period of 12.6 ± 3.4 months. These results are similar to the ESSENCE-DIABETES II trial conducted by Park et al.,[22] who observed rates of subacute and late thrombosis in diabetic patients undergoing implantation of zotarolimus- and sirolimus-eluting stents < 1% after 12 months of evolution.

Regarding the primary outcome of the trial, it was demonstrated that the occurrence of MACE was significantly lower in diabetic patients treated with DES, and the same occurred with death due to a cardiac cause and TVR. At first glance, these results appear to demonstrate that the use of DES in diabetics is related to better clinical outcome in the long-term, which requires caution in interpreting the data. When comparing the present results to those of other trials, it was observed that the majority of them presented no significant reduction in mortality or in other major cardiovascular outcomes in patients treated with DES, whether or not they were diabetic.[23,24]

Some trials have observed a reduction of stent thrombosis and AMI, but without a consistent reduction in the mortality rates with the use of this type of prosthesis, even with the second- or third-generation, so called due to their new metal platforms, more biocompatible and less thrombogenic polymers, and drugs with higher power of neointimal inhibition.[8,25]

Other observational trials and international registries, involving large numbers of diabetic and nondiabetic patients treated with DES, observed a reduction of ominous outcomes such as death and AMI, as well as in the rates of new revascularizations.[10,26,27] However, these results deserve reflection and must be viewed with caution, due to a possible selection bias and the relatively short duration of the clinical follow-up. In the present study, for instance, the multivariate analysis of the predictors for the occurrence of MACE took into consideration chronic renal disease and ACS, a fact fully demonstrated in the literature.[28] Coincidentally, these variables were significantly more present in patients treated with BMS, which was a disadvantage for this group and could explain the better results obtained in patients undergoing DES implantation. After adjustment of the multivariate analysis, no significant differences were observed in the rates of MACE between patients treated with and without DES at the end of one year of clinical follow-up (RR = 1.35; 95% CI: 0.87-2.10; P = 0.17).

The choice of BMS implantation in diabetic patients with ACS and renal failure – without doubt, patients at high risk for adverse events – can be questioned. Some possible explanations are: (1) DES are not routinely available in most public hospitals linked to the SUS; (2) the safety and efficacy of BMS for the treatment of patients with acute ischemic conditions, requiring urgent or emergent PCI, is equivalent to the safety and efficacy for DES, since in such cases the priority is the treatment of the culprit lesion, in order to reduce acutely events such as death and AMI; (3) in patients with ACS, the option of BMS use may be preferable, due to issues related to a lack of detailed knowledge of the patient's clinical history in terms of adherence to dual antiplatelet therapy, or even to the necessity of an early discontinuation of this therapy, due to non-cardiac comorbidities; and (4) in chronic renal patients, the use of BMS can be defended in view of a potential need for invasive non-cardiac procedures, such as the implantation of catheters or performing arteriovenous fistulas for dialysis and the possibility of a kidney transplant – situations in which a dual antiplatelet therapy may predispose to major bleeding.

Limitations

This was a nonrandomized trial, and therefore subject to selection bias; the follow-up period was relatively short for the analysis of the real differences in the occurrence of adverse cardiovascular events in diabetic patients; and no information regarding adhesion and duration of dual antiplatelet therapy was obtained, factors that could affect the incidence of adverse events, especially in patients treated with DES and in those with pre-PCI ACS.

CONCLUSIONS

In a population consisting of unselected diabetic patients treated by PCI, the use of DES was associated with significantly lower rates of major cardiovascular outcomes compared to BMS. However, after adjusting for confounding variables, the use of DES was not an independent predictor of major adverse cardiovascular events in the long-term.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

1. Luscher TF, Creager MA, Beckman JA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part II. Circulation. 2003;108(13):1655-61.
2. Iijima R, Ndrepepa G, Mehilli J, Markwardt C, Bruskina O, Pache J, et al. Impact of diabetes mellitus on long-term outcomes in the drug-eluting stent era. Am Heart J. 2007;154(4):688-93.
3. Abizaid A, Kornowski R, Mintz GS, Hong MK, Abizaid AS, Mehran R, et al. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. J Am Coll Cardiol. 1998;32(3):584-9.
4. Jiménez-Navarro MF, Curiel E, Hernández-García JR, Alonso Briales JH, Domínguez Franco A, Gómez Doblas JJ, et al. Influence of diabetes mellitus on clinical outcome after percutaneous coronary revascularization. Rev Esp Cardiol. 2002;55(4):365-71.
5. Lee TT, Feinberg L, Baim DS, Holmes DR, Aroesty JM, Carrozza JP Jr., et al. Effect of diabetes mellitus on five-year clinical outcomes after single-vessel coronary stenting (a pooled analysis of coronary stent clinical trials). Am J Cardiol. 2006;98(6):718-21.
6. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349(14):1315-23.
7. Sabate M, Jimenez-Quevedo P, Angiolillo DJ, Gomez-Hospital JA, Al-Fonso F, Hernandez-Antolin R, et al.; DIABETES Investigators. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial. Circulation. 2005;112(14):2175-83.

8. Bangalore S, Kumar S, Fusaro M, Amoroso N, Kirtane AJ, Byrne RA, 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.
9. de Waha A, Dibra A, Kufner S, Baumgart D, Sabate M, Maresta A, et al. Long-term outcome after sirolimus-eluting stents versus bare metal stents in patients with diabetes mellitus: a patient-level meta-analysis of randomized trials. Clin Res Cardiol. 2011;100(7):561-70.
10. Minha S, Bental T, Assali A, Vaknin-Assa H, Lev EI, Rechavia E, et al. A comparative analysis of major clinical outcomes using drug-eluting stents versus bare metal stents in diabetic versus nondiabetic patients. Catheter Cardiovasc Interv. 2011;78(5):710-7.
11. Moussa I, Leon MB, Baim DS, O'Neill WW, Popma JJ, Buchbinder M, et al. Impact of sirolimus-eluting stents on outcome in diabetic patients: A SIRIUS (SIRolImUS-coated Bx velocity balloonexpandable stent in the treatment of patients with de novo coronary artery lesions) substudy. Circulation. 2004;109(19):2273-8.
12. Patti G, Nusca A, Di Sciascio G. Meta-analysis comparison (nine trials) of outcomes with drug-eluting stents versus bare metal stents in patients with diabetes mellitus. Am J Cardiol. 2008;102(10):1328-34.
13. Kappetein AP, Head SJ, Morice MC, Banning AP, Serruys PW, Mohr FW, et al.; SYNTAX Investigators. 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(5):1006-13.
14. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, et al.; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med. 2012;367(25):2375-84.
15. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al.; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115(17):2344-51.
16. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124(23):e574-651.
17. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, et al. Guidelines on myocardial revascularization. Eur Heart J. 2010;31(20):2501-55.
18. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA. 2005; 293(17):2126-30.
19. van Werkum JW, Heestermans AA, Zomer AC, Kelder JC, Suttorp MJ, Rensing BJ, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol.2009;53(16):1399-409.
20. Centemero MP, Stadler JR. Stent thrombosis: an overview. Expert Rev Cardiovasc Ther. 2012;10(5):599-615. 21. Farinazzo MM, Cantarelli MJ, Castello Jr HJ, Gonçalves R, Giopatto S, Guimarães JBF. Intervenção coronária percutânea em diabéticos tratados com insulina. Rev Bras Cardiol Invasiva. 2013;21(1):43-8.
22. Park GM, Lee SW, Park SW, Kim YH, Yun SC, Cho YR, et al. Comparison of zotarolimus-eluting stent versus sirolimuseluting stent for de novo coronary artery disease in patients with diabetes mellitus from the ESSENCE-DIABETES II trial. Am J Cardiol. 2013;112(10):1565-70.
23. Simsek C, Räber L, Magro M, Boersma E, Onuma Y, Stefanini GG, et al. Long-term outcome of the unrestricted use of everolimus-eluting stents compared to sirolimus-eluting stents and paclitaxel-eluting stents in diabetic patients: the Bern-Rotterdam diabetes cohort study. Int J Cardiol. 2013;170(1):36-42.
24. Stenestrand U, James SK, Lindback J, Frobert O, Carlsson J, Schersten F, et al. Safety and efficacy of drugeluting vs. Bare metal stents in patients with diabetes mellitus: long-term follow-up in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Eur Heart J. 2010;31(2):177-86.
25. Garg P, Normand SL, Silbaugh TS, Wolf RE, Zelevinsky K, Lovett A, et al. Drug-eluting or bare-metal stenting in patients with diabetes mellitus: results from the Massachusetts Data Analysis Center Registry. Circulation. 2008;118(22):2277-85,7p following 2285.
26. Mulukutla SR, Vlachos HA, Marroquin OC, Selzer F, Holper EM, Abbott JD, et al. Impact of drug-eluting stents among insulin-treated diabetic patients: a report from the National Heart, Lung, and Blood Institute Dynamic Registry. JACC Cardiovasc Interv. 20081(2):139-47.
27. Kirtane A, Gupta A, Iyengar S, Moses J, Leon M, Applegate R, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. Circulation. 2009;119(25):3198-206.
28. Lehmann R, Fichtlscherer S, Schächinger V, Held L, Hobler C, Baier G, et al. Favorable long-term survival in patients undergoing multivessel-PCI compared to predicted prognosis of CABG estimated by EuroSCORE: procedural and clinical determinants of long-term outcome. J Interv Cardiol. 2009;22(6):511-9.