Diabetes Mellitus Impact in Patients Undergoing Percutaneous Coronary Intervention

Impacto de la diabetes mellitus en pacientes tratados con angioplastia coronaria

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ABSTRACT

Background: Diabetes mellitus (DM) has been associated with increased adverse outcomes in patients treated with percutaneous coronary intervention (PCI) compared with non-diabetic patients.
Objective: The aim of this study was to evaluate in a population of unselected patients treated with PCI, the risk of major adverse cardiac events (MACE) in diabetic patients stratified according to treatment (non-insulin dependent or insulin-dependent).
Methods: A retrospective, single center registry of patients with coronary artery heart disease treated with PCI was analyzed from March 2009 to June 2018 according to the presence of diabetes stratified into insulin-dependent DM (ID-DM) and non-insulin dependent DM (NID-DM), in line with the treatment received to control the metabolic disorder. An adjusted Cox regression model was applied to evaluate the relationship between the diabetic status and the risk of MACE.
Results: A total of 6,313 patients with mean follow-up of 4.1±1.8 years and a global prevalence of DM of 22.8% (NID-DM 19.1%, ID-DM 3.8%) were included in the study. Diabetic patients showed a higher risk profile, particularly those with ID-DM. At mean follow-up time, the adjusted risk of MACE was similar between Non-DM and NID-DM patients (HR 1.02 [0.81–1.27], p=0.85). A higher risk of MACE was reported in ID-DM compared with Non-DM (HR 1.73 [1.20–2.49], p=0.003) and NID-DM (HR 1.65 [1.10–2.48], p=0.015) patients. A significant interaction was observed between the diabetic status and the risk of cardiovascular events according to the indication of PCI at admission (pint 0.045).
Conclusions: In our registry of patients undergoing PCI and with a long-term follow-up, diabetic patients presented a high risk of MACE. This risk was particularly increased in ID-DM patients. However, there were no significant differences in the risk of MACE between NID-DM and Non-DM patients.

Key words: Diabetes Mellitus - Percutaneous Coronary Intervention - Angioplasty – Risk Factor - Risk Assessment

RESUMEN

Introducción: La diabetes mellitus (DM) se ha asociado a un incremento en los resultados adversos en pacientes tratados con angioplastia coronaria (ATC), en comparación con los pacientes no diabéticos.
Objetivos: Evaluar el riesgo de eventos cardiovasculares mayores en los pacientes diabéticos, estratificados según el tratamiento recibido (no insulinorrequirientes o insulinorrequirientes), en una población de pacientes no seleccionada tratados con angioplastia coronaria.
Material y métodos: Análisis de registro, unicéntrico y retrospectivo de pacientes con enfermedad coronaria tratados con ATC desde marzo 2009 a junio 2018, según la presencia de DM estratificada de acuerdo con el tratamiento establecido para el control del desorden metabólico en: DM insulino-requirientes (DM-IR) y DM no insulino-requirientes (DM-NIR). Se aplicó un modelo de regresión de Cox ajustado para evaluar la relación entre la presencia de diabetes y el riesgo de eventos cardiovasculares mayores.
Resultados: Se incluyeron 6.313 pacientes (seguimiento promedio 4,1 ± 1,8 años), con una prevalencia global de DM del 22,8% (DM-NIR 19,1%; DM-IR 3,8%). Los pacientes diabéticos presentaron un perfil de riesgo elevado, particularmente los DM-IR. Al seguimiento promedio, el riesgo ajustado de eventos cardiovasculares mayores fue similar entre los pacientes No-DM y los DM-NIR (HR 1,02 [0,81 – 1,27], p 0,85). En relación con los pacientes DM-IR, se observó un riesgo elevado comparados con los No-DM (HR 1,73 [1,20 – 2,49], p 0,003) y con los DM-NIR (HR 1,65 [1,10 – 2,48], p 0,015). Se observó una interacción significativa entre el estado diabético y el riesgo de eventos según la indicación de la angioplastia coronaria al ingreso (pint 0,045).
Conclusiones: En nuestra serie de pacientes tratados con angioplastia coronaria y con seguimiento a largo plazo, los pacientes diabéticos presentaron alto riesgo de eventos cardiovasculares mayores. Este riesgo se observó particularmente incrementado en pacientes DM-IR. Sin embargo, no se evidenciaron diferencias significativas en el riesgo de eventos entre los pacientes DM-NIR y los No-DM.

Palabras clave: Diabetes *mellitus* - Intervención coronaria percutánea - Angioplastia – Factores de riesgo - Medición de riesgo

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease with great impact on public health. Its prevalence has increased approximately fourfold in the last decades (1), it is one of the main causes of worldwide mortality and the costs allocated to its treatment are approximately twice higher than in non-diabetic patients. (2, 3)

In patients with cardiovascular disease, DM is one of the most prevalent risk factors after hypertension (HT) and dyslipidemia, (4) and is present in almost 30% of patients with coronary revascularization therapy. (5, 6)

Coronary heart disease in diabetic patients affects multiple territories, progresses rapidly and includes a higher prevalence of left main coronary artery (LMCA) disease, chronic total occlusions (CTO) and small vessel involvement (caliber <2 mm). (7, 8)

Numerous studies have shown that patients with DM and coronary artery heart disease have a higher rate of cardiovascular events compared with non-diabetic patients, regardless of the revascularization treatment. (4, 5)

The greater the severity of the metabolic disorder, the worse the prognosis of these patients (9). However, few studies have evaluated the differential risk of patients with DM treated with percutaneous coronary intervention (PCI), depending on whether they are treated or not with insulin, and the results are controversial.

The aim of this study was to evaluate in a population of unselected patients treated with PCI, the long-term risk of major adverse cardiovascular events (MACE) in diabetic patients stratified according to whether or not they required treatment with insulin to control their metabolic disorder.

METHODS

Database

This study is a database analysis of the Interventional Cardiology and Endovascular Therapeutics Service of Instituto Cardiovascular de Buenos Aires (ICBA), which provides information on patients undergoing surgery from 2009 to the present, enabling adequate follow-up at 30 days, and then, annually. This facilitates monitoring the surgical population characteristics and the short-, mid- and long-term clinical outcomes. The variables analyzed are: demographic data, comorbidities and cardiovascular history, administered treatment, procedure characteristics and in-hospital outcome, at 30 days and annually of more than 30,000 procedures.

Study population

Patients treated with PCI between January 2009 and June 2018 were included in the study. All statistical calculations were performed on the index procedure. The other procedures were classified as:
- *Deferred*. Coronary intervention scheduled for a second time.
   Events. An unscheduled new coronary intervention involving a previously revascularized lesion or a new lesion.

Patients with a diagnosis of cardiogenic shock (BP <100 mmHg, HR >100 bpm, poor peripheral perfusion with inotropic requirement and/or mechanical circulatory assistance) were excluded from the study.

Definitions

Regarding the severity of the metabolic disorder, patients were grouped into three categories:
- *Non Diabetics (Non-DM):* Patients without history of DM.
- *Non-insulin-dependent diabetics (NID-DM):* Patients with history of DM who are complying with hygienic-dietary treatment and/or oral medical treatment, without insulin.
- *Insulin-dependent diabetics (ID-DM):* Patients with history of DM who are administered insulin, regardless of whether or not they are receiving other therapeutic strategies (hygienic-dietary measures, oral antidiabetic agents).

Complete revascularization (CR) was defined as successful PCI in all lesions >70% present in vessels >2 mm. Patients with ≥1 significant residual lesion were considered to present incomplete revascularization (IR). Percutaneous coronary intervention was considered successful if a residual lesion <20% with TIMI 3 flow in the operated vessel was achieved.

According to the clinical condition at admission, patients were stratified into:
- *Stable patients:* Elective PCI in patients with stable angina >3 months.
- *Non-ST segment elevation acute coronary syndrome (NSTE ACS):* PCI in patients with unstable angina and non-ST-segment elevation electrocardiogram, with positive biomarkers (non-ST segment elevation acute myocardial infarction, NSTEMI) or negative biomarkers (unstable angina, UA).
- *ST segment elevation acute coronary syndrome (STE ACS):* PCI in patients in whom a primary, rescue or pharmacoinvasive PCI was performed within 24 hours of the onset of symptoms.

Clinical outcomes

A patient-oriented MACE composite, consisting of all-cause mortality, acute myocardial infarction (AMI), stroke and total revascularization (TRV) at mean follow-up was analyzed based on the recommendations of the Academic Research Consortium-2 (ARC-2) (10).

Stent thrombosis (ST) was defined according to the ARC-2. Total revascularization was described as the need for a new revascularization procedure, independently of whether it involved the previously treated vessel and/or coronary segment. Accordingly, TRV consisted of target lesion revascularization (TLR), which is the need for reintervention of a coronary segment previously treated with a stent±5 mm, target vessel revascularization (TVR), which is the need for reintervention of a coronary vessel previously treated with stent, regardless of whether the compromised segment has been treated with stent and finally, the revascularization of a previously untreated vessel (UTV). (10)

Statistical analysis

Qualitative variables are expressed as percentages and were evaluated by means of the chi-square test. Quantitative variables were subjected to normality tests (Kolmogorv-Smirnoff

test or Shapiro-Wilk test as appropriate, and asymmetry and kurtosis histogram parameters were measured). Variables that met normality criteria were expressed as mean±SD, or as median and interquartile range.

The risk of MACE, as well as that of its individual components at the end of the follow-up period or at 5 years, whichever occurred first, was assessed using Cox regression, with the Non-DM patient population as reference category. The analysis was adjusted for age, gender, HT, dyslipidemia, smoking, previous PCI, coronary artery bypass grafting (CABG), procedure year, previous AMI, chronic kidney failure (CKF), chronic obstructive pulmonary disease (COPD), clinical condition at admission, peripheral vascular disease (PVD), oral anticoagulation (OAC), left ventricular ejection fraction (LVEF), presence of multi-vessel disease and the implanted device. Regression confidence intervals were obtained by applying bootstrapping.

An interaction term between the diabetic state and the indication of PCI was generated to assess the influence of the clinical condition on the relationship between DM and the composite outcome.

The analysis was performed using SPSS statistical package (version 22, SPSS, IBM Corporation, Armonk, New York).

Ethical considerations
The study was evaluated and approved by the Ethics Committee and the Scientific Committee of ICBA, Instituto Cardiovascular, as it complied with treatment standards. In addition, all patients signed an informed consent during hospitalization, in which they accepted the anonymous use of their data for scientific research purposes.

RESULTS

Baseline characteristics
A total of 6,313 patients treated with PCI were evaluated; 77.1% were Non-DM, 19.1% NID-DM and 3.8% ID-DM (overall prevalence of DM: 22.8%), and mean follow-up was 4.1±1.8 years.

As shown in Table 1, diabetic patients had a higher prevalence of comorbidities, particularly those with ID-DM.

The characteristics of the procedure are detailed in Table 2. At admission, diabetic patients presented a higher prevalence of interventions for chronic stable angina (CSA). Clopidogrel was included more frequently in all groups as antiplatelet therapy. On the other hand, ID-DM patients presented the highest rate of ACO treatment with more frequent multivessel disease severity, as well as PCI to unprotected LMCA. There were no significant differences in the use of drug-eluting stents.

The results of the procedure showed that complete revascularization rate was lower in diabetic patients, particularly in those with ID-DM (Table 2).

Clinical outcomes
The overall MACE rate at mean follow-up was 206%; this was observed in 19.6% of Non-DM patients and 23.9% of DM patients (HR 1.24, 95% CI 1.12-1.41, p=0.001) (Figure 1A). Depending on the severity of the metabolic disorder, the MACE rate was 21.2% in

Table 1. Baseline population characteristics

	Non-DM (n=4,867)	NID-DM (n=1,208)	ID-DM (n=238)	p
Age±SD, years	69.1±11.4	71.5±10	69.5±9.9	<0.0001
Male gender, %	82	83.7	81.5	0.35
Cardiovascular risk factors				
Hypertension, %	71.8	86	87.7	<0.0001
Dyslipidemia, %	74.5	83.7	83.5	<0.0001
Obesity, %	13.2	23.5	30.1	<0.0001
Hereditary diseases, %	18.3	13.4	14	<0.0001
Ex-smokers, %	42.7	46.6	50.4	0.004
Current smokers, %	17.6	12.4	11.4	<0.0001
Cardiovascular history				
Percutaneous coronary intervention	26.3	34.7	35.2	<0.0001
Coronary artery bypass grafting	11	18.6	24.6	<0.0001
Acute myocardial infarction	16.3	20.6	24.6	<0.0001
Stroke, %	2.9	4.3	6.8	0.001
Atrial fibrillation, %	2.8	2.2	5.1	0.053
Peripheral vascular disease	6	9.7	14.4	<0.0001
History of hemorrhage	1	1.5	3.4	0.03
Moderate/severe aortic stenosis	3	3.6	3.8	0.467
Other previous disaesss				
Chronic kidney failure, %	2.6	4.9	9.3	<0.0001
Dialysis,%	0.3	0.4	0.8	0.305
Chronic obstructive pulmonary disease, %	3.5	2.8	3.8	0.506
Ejection fraction <30%	4.5	4.9	8.3	0.055

Non- DM: Non-diabetics. NID-DM: Non-insulin-dependent diabetics. ID-DM: Insulin-dependent diabetics.

	Non-DM (n=4,867)	NID-DM (n=1,208)	ID-DM (n=238)	p
Clinical presentation				
Chronic angina,%	42.1	48.7	51.4	<0.0001
NSTE ACS, %	42.8	41.6	38.7	0.485
STE ACS, %	15.1	9.7	9.9	.
Medical treatment				
Clopidogrel, %	72.3	76.2	80.5	0.002
Prasugrel, %	11.6	11.3	8.9	0.529
Ticagrelor, %	16.1	12.5	10.6	0.001
IIb/IIIa inhibitors, %	3.8	2.1	2.5	0.009
Oral anticoagulation, %	4.7	5.2	10.2	0.001
Coronary disease extension				<0.0001
1 vessel, %	47	40.5	33.7	
2 vessels, %	31.3	33.5	32.7	
3 vessels, %	16.3	19.5	23.6	
LMCA + multiple vessels, %	5.4	6.5	10.1	
Implanted devises				0.205
Drug-elluting stents	95.2	96.2	97.9	
Everolimus-eluting stent, %	33.9	34.5	29.8	
Zotarolimus-eluting stent, %	30.3	31.1	36.1	
Sirolimus-eluting stent, %	10	9.6	16	
Others, %	21	20.9	16	
Bare-metal stents, %	4.7	3.6	2.1	
Balloon, %	0.1	0.2	0	
Procedure results				
Successful PCI	97.6	97.4	97.5	0.929
Complete revascularization	75	67.7	62.7	<0.0001
Intraangioplasty complicationsµ, %	2.6	2.4	3.8	0.467

Table 2. Procedure characteristics

NSTE ACS: Non-ST-segment elevation acute coronary syndrome. STE ACS: ST-segment elevation acute coronary syndrome. LMCA: Left main coronary artery. PCI: Percutaneous coronary intervention. µ Intraangioplasty complications: residual dissection, no-reflow phenomenon, coronary perforation, stent deformation.
Non- DM: Non-diabetics. NID-DM: Non-insulin-dependent diabetics. ID-DM: Insulin-dependent diabetics.

NID-DM and 37.8% in ID-DM patients. Compared with Non-DM patients, the adjusted risk of MACE at mean follow-up was significantly higher in ID-DM patients (HR 1.73, 95% CI 1.20-2.49, p=0.003), while those with NID-DM presented a similar risk (HR 1.02, 95% CI 0.81-1.27, p=0.85) (Figure 1B; Table 3).

Table 3 shows the cumulative event rate and the adjusted risk for each comparison. It can be seen that the group of ID-DM patients presented a higher risk of overall mortality, AMI and need for new revascularizations when compared with Non-DM and NID-DM.

The following observations stand out in the analysis of the individual components of TRV:

Compared with non-DM patients, both NID-DM and ID-DM showed a high risk of therapeutic failure in the target vessel and the target lesion (Table 3).

The overall incidence of ST was 0.7%. In this case the risk was significantly higher in NID-DM and ID-DM patients compared to Non-DM. In turn, patients with ID-DM had a higher risk of ST than NID-DM.

A significant interaction was observed between the clinical condition and diabetic patients with respect to the incidence of MACE (Figure 2). In patients with

CSA, those with DM did not present a higher risk of events compared with Non-DM (OR 0.90, 95% CI 0.72 - 1.13, p=0.89). However, in the framework of ACS, diabetic patients presented an increased risk of MACE (OR 1.25, 95% CI 1.04-1.50, p=0.02) (pint 0.045).

DISCUSSION

In this analysis with long-term follow-up of an unselected population of patients treated with PCI, the following observations can be highlighted: a) the prevalence of DM is almost 23%; b) diabetic patients had a higher rate of comorbidities than non-DM patients, particularly those with ID-DM; c) patients with ID-DM presented a higher risk of MACE compared with Non-DM and NID-DM patients and d) patients with NID-DM presented a similar risk of MACE than Non-DM patients.

Diabetes mellitus is a worldwide epidemic favored by the rapid increase in obesity, sedentary lifestyle, and population aging. (11, 12) In addition to its high morbidity and mortality (13, 14) and the high care-related costs (2, 3), the control of this entity represents an important challenge for public health.

Fig. 1. Adjusted risk graphs of MACE at mean follow-up. Figure 1**A** shows the comparison between DM (red line) vs. Non-DM (dotted line) patients. Figure 1**B** shows the comparison according to the diabetic status; an increased risk of events is observed in ID-DM patients (red). On the other hand, NID-DM patients (uneven line) presented a similar risk to Non-DM patients (dotted line). Non- DM: Non-diabetics. NID-DM: Non-insulin-dependent diabetics. ID-DM: Insulin-dependent diabetics.
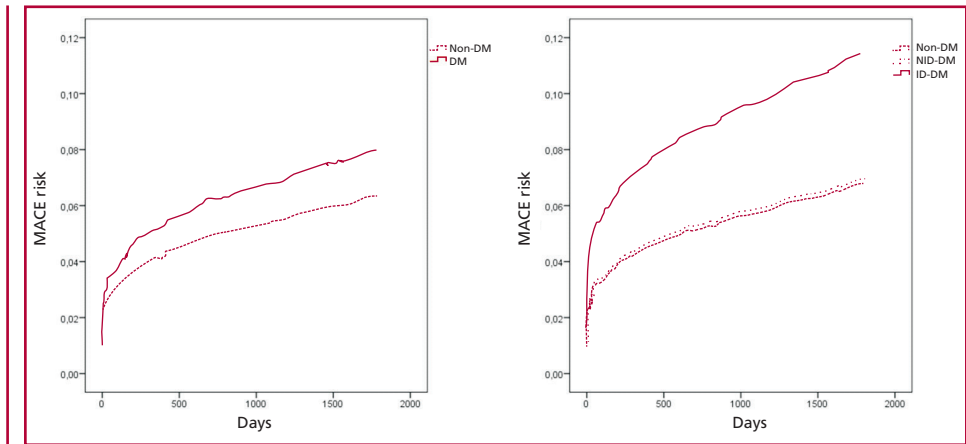

Table 3. Clinical results

	Cumulative Event Rate			Hazard Ratio (95% CI)		
	Non-DM (n=4,867)	NID-DM (n=1,208)	ID-DM (n=238)	NID–DM vs. Non-DM	ID–DM vs. Non-DM	ID-DM vs. NID-DM-
MACEa, %	19.6	21.2	37.8	1.02 (0.8-1.3), p 0.8	1.7 (1.2-2.4), p 0.003	1.6 (1.1-2.5), p 0.015
Mortality, %	5.7	7.6	14.3	1.1 (0.9-1.5), p 0.3	3.1 (2.1-4.5), p <0.0001	2.7 (1.8-4.2), p <0.0001
AMIb, %	3	2.6	5.1	0.7 (0.5-1.2), p 0.1	1.1 (0.6-2.2), p 0.8	1.5 (0.7-3.3), p 0.3
STROKEc, %	0.5	0.7	0.8	2.0 (0.8-4.8), p 0.1	1.9 (0.4-8.6), p 0.4	1.3 (0.3-6.2), p 0.7
TRVd, %	12.9	13.1	23.1	1.0 (0.7-1.1), p 0.8	1.7 (1.2-2.3), p 0.001	1.9 (1.3-2.8), p <0.0001
TVRe, %	5.4	7.5	15.5	1.3 (0.9-1.7), p 0.09	2.8 (1.9-4.1), p <0.0001	2.3 (1.4-3.5), p <0.0001
TLRf, %	2.9	4.1	9.7	1.6 (1.1-2.3), p 0.01	3.5 (2.1-5.9), p <0.0001	2.2 (1.2-3.5), p 0.01
UTVRg, %	8	5.5	7.6	0.6 (0.5-0.8), p 0.002	0.8 (0.5-1.5), p 0.5	1.4 (0.7-2.6), p 0.3
STh, %	0.4	1.5	3.8	4.1 (2.0-8.3), p <0.0001	9.6 (3.8-24), p < 0.0001	2.46 (1.08-5.60), p 0.03
Major bleeding, %	1.2	1.7	2.1	1.11 (0.60-2.05), p 0.7	1.66 (0.55-4.79), p 0.4	1.24 (0.45-3.39), p 0.6

[a] MACE: mortalidad/AMI/STROKE/TRV [b] AMI: acute myocardial infarction; [c] Stroke; [d] TRV: total revascularization; [e] TVR: target vessel revascularization; [f] TLR: target lesion revascularization; [g] UTVR: untreated vessel revascularization, [h]ST: stent. thrombosis
Non- DM: Non-diabetics. NID-DM: Non-insulin-dependent diabetics. ID-DM: Insulin-dependent diabetics.

Fig. 2. Interaction analysis between diabetes and MACE occurrence based on the indication of coronary angioplasty. The interaction was statistically significant (pint 0.045). PCI: Percutaneous coronary intervention. CA: chronic angina. ACS: acute coronary syndrome.

Non- DM: Non-diabetics. NID-DM: Non-insulin-dependent diabetics. ID-DM: Insulin-dependent diabetics.
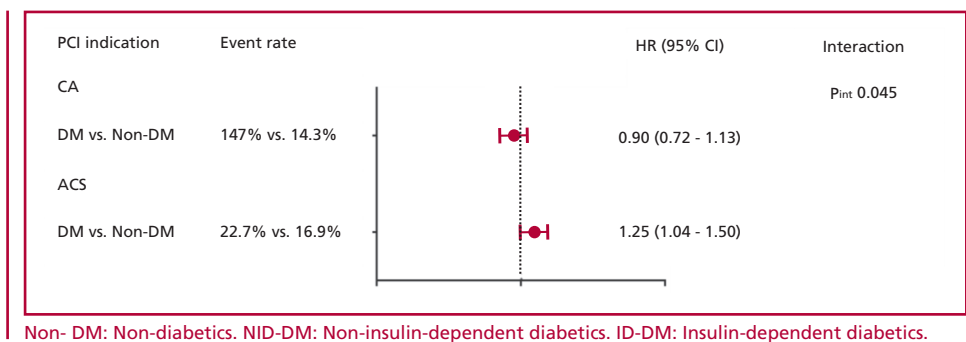
According to the *Third National Survey of Risk* Factors published by the Ministry of Health of the Argentine Republic (15), in 2014 the prevalence of DM was 9.8%, which meant an increase of 13% with respect to 2005, and in the patient segment ≥65 years the prevalence was 20.3%. In this study, average age was almost 69 years and the overall prevalence of DM was approximately 23%, 83% NID-DM and 17% ID-DM.

Coronary heart disease in the diabetic patient is characterized by being diffuse and rapidly progressive. (8) In our series, diabetic patients had higher rates of multi-vessel disease, with an increased prevalence of LMCA disease, as described in Table 2. It has been reported that the greater the severity of the metabolic disorder, the greater the extent of the disease. In a population of 3,805 patients, it was shown that high

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glycosylated Hb values were independently associated with a higher SYNTAX score. (9)

In our case series with a follow-up of 4.1±1.8 year, 20.6% of the patients developed at least one cardiovascular event. The rate of MACE at mean follow-up was significantly higher in DM patients (23.9% vs. 19.6%, p=0.001). This tendency has been previously reported and has not changed significantly with the implementation of second generation drug-eluting stents. (16, 17) In this sense, an observational study that included 3,026 patients treated with second-generation drug-eluting stents compared the outcome of DM vs. Non-DM patients. Results showed that diabetic patients presented 1.4 times higher risk of MACE compared with Non-DM patients. (18)

According to the diabetic condition of the population, patients with ID-DM presented a differential risk of MACE, compared with NID-DM and Non-DM patients. This group presented a higher cardiovascular risk profile, with greater prevalence of comorbidities (Table 1).

Taking into account these significant differences in baseline characteristics, the adjusted risk of MACE has been almost 2 times higher in the ID-DM group compared with the other study groups (Table 3, Figure 1). It is possible to explain the differential risk in this group of patients based on an uneven distribution of cardiovascular risk factors, as well as in the pathophysiology of this entity that predisposes to a greater vulnerability of atheromatous plaque [19] and to a prothrombotic and proinflammatory state mediated by insulin. (7, 20, 21)

Similarly, this greater predisposition to develop systemic atherosclerotic disease mitigates the advantageous effects of devices with focal action, such as stents. These results are similar to other reports in the literature. (5, 18, 22-25)

According to estimates derived from a sub-analysis of the SCAAR registry (Swedish Coronary Angiography and Angioplasty Registry) that included 58,891 patients (19% diabetic), ID-DM patients presented a twofold increased risk of MACE than Non-DM patients, similar to the results found in this work. (5)

At present there is a controversy regarding the evolution of NID-DM compared with Non-DM patients. In our investigation we have not observed significant differences between both groups of patients regarding the risk of MACE at long-term follow-up. In accordance with these results, a sub-analysis of the Tokyo-MD PCI study on 1,866 patients found that the 3-year risk of MACE was similar both in NID-DM and Non-DM patients. (2, 3)

In an unselected cohort of 9,313 patients, Noman et al. observed that NID-DM patients did not present a differential risk compared with Non-DM patients in the long-term (OR 1.15, 95% CI 0.89-1.49). (22) Conversely, the SCAAR registry showed that NID-DM patients behaved as an intermediate risk group for MACE between ID-DM and Non-DM patients at approximately 3 years, (5) while Pi et al. showed similar results in patients treated exclusively with second generation drug-eluting stents. (18)

A recent meta-analysis, conducted by Li et al. including 12 studies with 52,451 patients, showed that NID-DM patients presented 19% higher risk of MACE, mainly at the expense of a higher TVR rate, without significant differences in terms of mortality. (26)

In the incidence of MACE we observed a significant interaction between diabetes and the clinical condition that motivated PCI (Figure 2). While in stable patients no significant differences were observed, in patients with ACS the risk of events was greater in patients with DM. In diabetics, the incidence of ACS was almost 30% (27) and as expected, this proportion will increase with the epidemiological expansion of the disease. (28, 29)

In patients with DM and ACS, less use of evidence-based therapies has been reported (30), with less frequent revascularization and greater delay to its implementation since the beginning of the event. (31) In addition, because of the frequent atypical presentations of symptoms, it has been observed that diabetic patients often delay in seeking medical care. (32)

In a series of 6,385 patients enrolled in The Second Euro Heart Survey on Acute Coronary Syndromes (EHS-ACS-II), diabetic patients with ACS presented a higher risk profile, with greater extent and severity of coronary heart disease. (30) Although DM was not an independent predictor of in-hospital mortality, a higher mortality rate was observed in the long-term follow-up.

Moreover, a sub-analysis of the Framingham and Fast Revascularization during Instability in Coronary artery disease II (FRISC II) study showed that diabetic patients with ACS had a higher mortality or AMI rate than Non-DM patients. (33) In turn, diabetic patients presented greater benefit with an early revascularization strategy, with a number needed to treat (NNT) of 11 to prevent one death or AMI, compared with a NNT of 32 for Non-DM.

Diabetes mellitus is a clear predisposing factor for new revascularizations. (26, 34) In our series, ID-DM patients presented an increased risk of new revascularizations, while non-significant differences were observed between NID-DM and Non-DM patients (Table 3). While the former presented a higher risk of failure in the treated lesions (TVR and TLR), Non-DM patients presented a higher risk of new revascularizations in the UTV. The implementation of second generation drug-eluting stents has significantly improved PCI results, with a reduction in clinical and angiographic restenosis rates compared with first generation drug-eluting stents. (35-37)

Although there is controversy over the most appropriate device in diabetic patients, a meta-analysis, conducted by Bangalore et al., which included 42 studies with 22,844 patients, showed that in these

patients, drug-eluting stents in general presented a significant reduction in the need for new revascularizations compared with bare-metal stents, while everolimus-eluting stents were the safest and most effective devices (38)

An increased risk of ST was observed in general in patients with DM, with particularly high rates in the group of patients with ID-DM (Table 3). However, the evidence in this regard is controversial. Some reports suggest an exclusively high risk in the group of patients with ID-DM (18, 22), while other authors have reported a similar risk among the three groups. (23, 25) One aspect that must be taken into account is that the use of more potent antiplatelet agents than clopidogrel has reduced ST rates (39, 40), which could be especially useful in the pro-inflammatory state of diabetic patients. However, similarly to our experience, numerous series have reported that clopidogrel is the antiplatelet agent most frequently used in this population.

Limitations
Our study presents certain noteworthy limitations. First, there are limitations inherent to non-randomized comparisons, such as selection bias, the heterogeneous distribution of risk factors and the possible existence of unmeasured confounding factors, even after conducting a multivariate analysis adjusted for identified differences.

Our study is dedicated to assessing the impact of DM according to treatment or not with insulin in patients undergoing only PCI in the current period (from 2009 to the present). Therefore, patients (diabetic or not) who received medical treatment or myocardial revascularization surgery are not included in this analysis and our results do not allow conclusions on this topic.

In our center follow-up coronary angiography is not systematically performed in the absence of evidence that demonstrates clinical benefits in the long-term follow-up. For this reason, in the evaluation of intrastent restenosis, only clinically relevant cases were detected.

Finally, data regarding the type of oral hypoglycemic agent used, or the duration and dose of insulin treatment, are not available in our database.

CONCLUSION
In our series of unselected cases treated with PCI and long-term follow-up, diabetic patients presented a high risk of major cardiovascular events, as well as events related to the implantation of coronary stents (intrastent restenosis and intrastent thrombosis). This risk was particularly high in ID-DM patients. However, there were no significant differences in the risk of events between NID-DM and Non-DM patients. These results could contribute to individualize in decision-making the most appropriate revascularization strategy for each patient.

Conflicts of interest
None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material).

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