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NON–ST-ELEVATION MYOCARDIAL INFARCTION (NSTEMI) OUTCOMES IN TYPE 2 DIABETIC PATIENTS WITH NON-OBSTRUCTIVE CORONARY ARTERY STENOSIS: DIABETIC MYOCARDIAL INFARCTION CORONARY NON-OBSTRUCTIVE STENOSIS: DIA-MYCONOS STUDY.

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ABSTRACT

Objective: Management of type 2 diabetic patients (DMT2) with non-obstructive coronary stenosis (NOCS) Non–ST-Elevation Myocardial Infarction (NSTEMI) is unclear**.** We evaluate the 12-month prognosis of DMT2 with NOCS-NSTEMI and compared them with a cohort of DMT2 with NSTEMI and obstructive coronary stenosis (OCS) treated with percutaneous coronary intervention (PCI). **Methods:** DIAbetic MYocardial COronary Non-Obstructive Stenosis (DIA-MYCONOS) was an observational study prospective study of NSTEMI DMT2 patients undergoing angiographic study. 1098 DMT2 patients with first NSTEMI undergoing coronary angiography were studied. Patients were categorized in two groups, either with or without OCS (stenosis ≥50%). OCS patients were treated with PCI and optimal medical therapy (n=922, 84%). NOCS patients were treated with optimal medical therapy alone (n=176, 16%). Endpoints included cardiac mortality, all-cause mortality and re-hospitalization for coronary disease and heart failure. **Results:** OCS-NSTEMI patients were undergoing to PCI plus medical therapy, whereas NOCS-NSTEMI patients were treated with medical therapy. Groups received similar secondary prevention therapies. 1098 patients were followed-up for 1 year. In-hospital mortality was similar (1.11 vs. 1.14%), and 1-year total mortality was 6.72% in NSTEMI patients with OCS treated with PCI and 11.93% in NSTEMI patients with NOCS treated with medical therapy (P<0.09). 18.3% of NSTEMI patients with OCS and 36.9% of NSTEMI patients with NOCS were re-hospitalized for cardiovascular diseases (P <0.05). **Conclusions:** NOCS-NSTEMI-DMT2 patients treated with medical therapy have poor prognoses as compared with OCS-NSTEMI patients treated with PCI, despite a less aggressive initial atherosclerosis. These findings evidence a possible gap in the NOCS-NSTEMI management.

KEYWORDS: diabetes, myocardial infarction, coronary stenosis.

INTRODUCTION

Patients with diabetes mellitus have a twofold to fourfold likelihood of developing coronary artery disease (CAD) with marked morbidity and mortality.[1] CAD accounts for 75% of all deaths in patients with diabetes mellitus, and approximately 20% to 25% of all patients with Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI) have diabetes.[2] Patients with UA/NSTEMI and diabetes have more severe CAD and adverse outcomes (death, MI, or readmission with UA at 1 year) compared to non-diabetic patients.[2] Contemporary management strategies of NSTEMI are

based on the early angiographic studies who have demonstrated a non-obstructive coronary stenosis (NOCS) in almost half of these patients.[3] A recent detailed systematic review[4] demonstrates that diabetes mellitus has a 16% prevalence of MI with NOCS presentations. In this context, patients with diabetes and NOCS-NSTEMI represent a conundrum because there are no proper indications regarding the management of these patients. Indeed, according to the recent guidelines[5], diabetic patients with obstructive coronary stenosis (OCS) (stenosis ≥50%) NSTEMI, as non-diabetic patients, are usually treated with percutaneous coronary intervention (PCI) and medical therapy. On the contrary, diabetic patients with NOCS-NSTEMI, as non-diabetic patients, are usually treated with medical therapy, as nitrates, dual antiplatelet therapy, beta-blockers etc.[6] Furthermore, whether they have similar clinical features and outcomes as diabetic patients with NSTEMI and obstructive CAD treated with drug-eluting stents or bare metal stent is still unclear.[7, 8] Accordingly, the primary objectives of this observational study was to evaluate the 12-month prognosis of diabetic patients with NSTEMI and NOCS. We investigated this prospectively in a cohort of diabetic patients with NSTEMI and NOCS and compared them with a cohort of diabetic patients with NSTEMI and OCS treated with PCI.

METHODS

Patients

Consecutive type 2 diabetic patients[9] with first NSTEMI, referred for coronary angiography at the Department of Cardiology of the Cardarelli Hospital in Naples (Italy), Unit of Cardiology, "S. Maria della Misericordia" Hospital, Sorrento, Naples (Italy) and at Department of Cardio-Thoracic and Respiratory Sciences, Second University of Naples (Italy), between January 2007 and January 2012 were entered in a database prospectively. Inclusion criteria included: age of 18 years or greater, presentation to the cardiac catheterization laboratory for coronary angiography in the setting of first NSTEMI, type 2 diabetes diagnosis according to the American Diabetes Association criteria: fasting glucose level of ≥7 mmol/L, symptoms of diabetes and casual plasma glucose of ≥11.1 mmol/L, or the need for oral hypoglycemic agents or insulin.[1] All NSTEMI patients were referred to the cardiac catheterization laboratory within 24 h of clinical presentation. Patients with no coronary disease detected by coronary angiography, left ventricular ejection fraction less than 25%, previous myocardial infarction, previous PCI or/and coronary by-pass grafting, Tako-tsubo cardiomyopathy, myocarditis and stroke were excluded. Other exclusion criteria were contraindications to contrast agents and impaired renal function (GFR <60 mL/min/1.73m2 assessed by MDRD formula). Patients were categorized in two groups, either with or without obstructive coronary stenosis. NOCS patients were defined as the presence of an NSTEMI with non-obstructive coronary artery disease (1-49% luminal stenosis). NSTEMI patients with significant obstructive coronary artery disease (at least 1 stenosis ≥50%) were designated as OCS patients. Patients with OCS were referred for invasive diagnostics with the intention of performing PCI if indicated: symptom duration of 24 hours or less and coronary angiographic stenosis ≥50%, independently of ECG signs suspects for ischemia but mandatorily without ST elevation. Patients with NOCS after angiographic study were referred for medical therapy: symptom duration of 24 hours or less, absence of stenosis ≥50%, and none significant ST elevation.[10] All patients were included in the study after they gave written informed consent. Routine analyses were obtained on admission before coronary angiography and before full medical therapy was started. The investigation conforms with the principles outlined in the Declaration of Helsinki for use of human tissue or subjects. The Institutional Review Board approved the protocol.

Study protocol

Quantitative Coronary Angiography. Upon emergency wards admission, all patients will be assigned to undergo prompt coronary angiography. The analyses of all angiographic data before and after the PCI procedure were performed by expert operators (Toshiba, Infinix CS-i). In order to determine the vessel reference diameter, three measurements in a coronary segment without atherosclerotic disease were performed. The luminal diameter of the coronary artery and the degree of stenosis were measured before dilation and at the end of the procedure according TIMI score. Vessel size refers to the reference diameter of the relevant coronary segment and is represented by the interpolated reference diameter pre-PCI because this is the closest and most objective approximation of the disease-free vessel wall. Minimum luminal diameter (MLD) is the point of maximal luminal narrowing in the analyzed segment.[2] In case of multivessel coronary artery disease we tried to treat the identifiable culprit lesion. In case of not identifiable culprit lesion, we treated lesions suitable for PCI. We may report a ratio between the numbers of PCIs and coronary angiograms about 0.5. The namely stents type used are: DES Resolute endeavor (Medtronic)/ Xience V (ABBOT); BMS Pro Kinetic (Biotronic) Chrono (Sorin) (Stents length: < 32 mm; Stents diameter: >2.25mm 4.25mm).

Blood glucose control in emergency wards. After coronary angiography procedures, all hyperglycemic patients (blood glucose ≥ 180 mg/dl) were treated with intensive glucose control to keep blood glucose levels between 140 and 180 mg/dl, as previously described.[11] Continuous insulin infusion of 50 IU Actrapid HM (Novo-Nordisk) in 50 ml NaCl (0.9% using a Perfusor-FM-pump) was started only when blood glucose levels exceeded 180 mg/dl and adjusted to keep blood glucose between 140 and 180 mg/dl. When blood glucose fell <140 mg/dl, insulin infusion were tapered and eventually stopped. After the start of insulin infusion protocol a glycemic control was provided every hour in order to

obtain three consecutive values that were within the goal range. The infusion lasted until stable glycemic goal (140-180 mg/dl) for at least 24 h. After that glycemic goal was maintained for 24 h, the infusion was stopped and subcutaneous insulin was initiated. Insulin was given as short-acting insulin before meals and long-acting insulin in the evening throughout the period of hospital stay. In patients without stress hyperglycemia (blood glucose <180 mg/dl) multidose insulin therapy was used aimed to obtain fasting glucose comprised from 90 to 130 mg/dl and post-prandial glucose <180 mg/dl. With regard to the full medical therapy, the protocol stated that the use of concomitant treatment should be as uniform as possible and accorded to evidence-based European guidelines for NSTEMI.[12] Detailed descriptions of the blood glucose control are provided in the Supplementary Appendix.

Follow-up

After discharge from the hospital, all patients were managed and followed quarterly for 12 months after event, as outpatients, to perform clinical evaluation, routine analyses and cardiovascular evaluation (ECG, exercise ECG, echocardiography, exercise myocardial scintigraphy), as well as, with the goal to maintain HbA1c level at <7%, fasting blood glucose level of 90-140 mg/dl and post-prandial blood glucose level of <180 mg/dl.

Echocardiographic assessment. At admission, six and 12 months after NSTEMI, patients underwent two-dimensional echocardiography as previously described.[13] The study was performed with a standardized protocol and phased-array echocardiographs with M-mode, 2-dimensional and pulsed, continuous-wave and color flow Doppler capabilities. The ejection fraction was calculated from area measurements with the area-length method applied to the average apical area.[3] The left ventricular internal dimension and interventricular septal were measured at the end diastole and end systole, and the wall motion score index was calculated according to American Society of Echocardiography recommendations.[3]

Gated myocardial perfusion single-photon emission computed tomography (MPS). 12 months after MI, all patients underwent dual-day Tc-99 m sestamibi rest and stress gated MPS by exercise or dipyridamole (if exercise was not performable) stress test, according to the Society of Nuclear Medicine recommendations.[14] SPECT imaging was performed with dual-head gamma cameras equipped (Siemens Erlangen- Germany) with low energy high-resolution collimators. A 15% window was centered on the 140 photopeak for 99Tc-MIBI. An automated software program was used to the scores incorporating both the extent and severity of perfusion defects, using standardized segmentation of 20 myocardial regions. Each myocardial segment was scored from normal (score = 0) to absent perfusion (score = 4). The Summed Stress Score (SSS) was obtained by adding the scores of the 20 segments of the stress images. A same method was applied to the resting images to calculate the summed rest score (SRS). The Summed Difference Score (SDS) represents the difference between the stress and rest scores and is taken to be an index of ischemic burden. Patients were considered to have an abnormal MPS with a SSS >3. Significant ischemia was defined by a SDS>2 and classified as mild/moderate (2 to 6) and severe (>6)

Cardiovascular endpoints

The primary end point for both groups consisted of cardiovascular events, defined as the myocardial infarction, hospitalization for heart failure and unstable angina, or cardiac mortality. All deaths were reviewed and classified as cardiac (death caused by acute myocardial infarction, ventricular arrhythmias, or refractory heart failure) or non-cardiac.[12] The secondary endpoint consisted of reduced ejection fraction, and reduction in coronary perfusion.

Statistical analyses

Statistical methods. These groups were compared using the Pearson $\chi 2$ test for categorical variables and the Kruskal-Wallis test for continuous variables. Candidate covariates for entry into the multivariable model were identified by focusing on factors that differed significantly ($P<0.05$) in the univariate analyses between patients with OCS-NSTEMI and NOCS-NSTEMI. Cox regression was used to construct the mortality model. The HRs for mortality were adjusted for age, BMI, diabetes duration, smoking status, heart rate, use of aspirin, hs-cTnT levels, cholesterol levels, LDL-cholesterol levels and tryglycerides levels at baseline, and the administration of aspirin, thienopyridines, association of both anti-aggregant therapy, β-blockers, ACE inhibitors or ARBs, anti-hyperglycemic and hypolipidemic therapy during hospitalization for NSTEMI. Survival analysis through the first year following NSTEMI was performed using the Kaplan-Meier and method Cox regression methods. Mortality curves were generated separately for patients with OCS-NSTEMI and NOCS-NSTEM and then compared using the log-rank test. All tests were two-sided and considered statistically significant at <0.05. Odds ratios are reported with 95% confidence intervals. All analyses were performed using SPSS version 21 (SPSS). All analyses were performed in 2 populations: all patients with OCS-NSTEMI treated with medical therapy and PCI, and patients with NOCS-NSTEMI treated with medical therapy.

RESULTS

Study population

Two centers in Italy enrolled consecutive patients into the DIA-MYCONOS study between December 2007 and March 2012 according to inclusion criteria. A total of 1558 diabetic patients were admitted to emergency wards for NSTEMI according to the AHA definition.[12] Of these, 1098 (OCS= 922 patients; NOCS= 176 patients)

were enrolled and included in the study analysis (Figure 1). The majority of patients presented with OCS-NSTEMI (84%), whereas the remaining patients were diagnosed with NOCS-NSTEMI (Table 1). In the overall population, OCS-NSTEMI was associated with older age, higher percentage of smoking patients, higher body-mass index, higher diabetes duration, higher triglyceride levels, higher levels of low-density lipoprotein (LDL), higher cholesterol levels, and higher troponin T levels (Table 1). The median time between symptom onset and the start of angiography procedure at hemodynamic unit was 7.1 ± 2.1 h in patients with OCS-NSTEMI and 6.9 ± 0.77 h in those with NOCS-NSTEMI. Number and severity of lesions and percentage of patients with 2 and 3 coronary vessel diseases were significantly higher in OCS-NSTEMI than NOCS-NSTEMI patients (Table 1). In OCS-NSTEMI group, 69% of the patients were treated with drug-eluting stents and 31% of patients were treated with bare metal stents (Table 1).

In-hospital treatments and glucose control

During hospital stay, aspirin was administered to 96% of patients and statins to 75% in both groups. Beta-blockers were given to 75% of patients and 40% received an ACE-inhibitor in both groups. Among whole population, 82% of the patients were treated with association between thienopyridine and aspirin: 81.9% of OCS-NSTEMI patients and 69.9% of NOCS-NSTEMI patients. The mean plasma glucose level during the peri-angiographic period was similar in the groups (OCS, 172.9±16.4 vs. NOCS, 176.1±15.4 mg/dl). Moreover, glycemic goal was maintained for 24 h in both groups (OCS, 167±10 mg/dl; NOCS, 162±12; mg/dl). Blood glucose <70 mg/dl with and without symptoms occurred during the insulin infusion in the 10% of OCS patients and in 11% of NOCS patients. At hospital discharge, both fasting and post-prandial plasma glucose levels were similar in the groups (OCS, fasting, 137±26 mg/dl, post-prandial 179±18mg/dl; NOCS, 141±24 mg/dl, post-prandial 181±23 mg/dl). At discharge from hospital, the rate of the use of ACE-inhibitors, aspirin, beta-blockers, statins, and thienopyridines increased compared to their use at admission in both OCS and NOCS population. At hospital discharge, all patients were managed and followed as outpatients for 12 month after the event.

Treatments and glucose control at 12 months following discharge

Over the 1 year follow-up period, mean of fasting, post-prandial plasma glucose and HbA1c levels were similar in the two groups (P=NS for all) (Table 1). There was no difference in hypoglycemic therapy during the follow up among the groups. At 1 year, the patients' BMI was 26.9±2.1 in OCS patients and 26.8±1.8 in NOCS patients (Table 1). Pharmacological medications being taken at 1-year follow-up are shown in Table 1. Dual anti-aggregant therapy were higher in OCS-NSTEMI patients than NOCS-NSTEMI patients (Table1).

In-hospital and post-discharge outcomes

Of the 1098 patients who were enrolled in the study, 12 (1.1%:) died while in hospital. The in-hospital mortality rate did not differ between patients with OCS (1.14%) or NOCS (1.11). However, 21 (2.28%) of the OCS patients and 4 (2.27%) of the NOCS patients had recurrent ischemia or extension to a Q-wave myocardial infarction. The unadjusted Kaplan-Meier estimated survival curve is shown in Figure 2. The all death rate at 1 year was 11.9% in patients with NOCS-NSTEMI vs. 6.7 % in OCS-NSTEMI (P <0.01) (Figure 2A). The Kaplan–Meier mortality curve for the NOCS patients diverged early from the curve for the OCS groups. After 1 year of event, survival was 93.3% and 88.1% in patients with OCS-NSTEMI and NOCS-NSTEMI, respectively. Furthermore, we categorized causes of death into cardiovascular death. The point estimates indicated a stronger association between both NOCS-NSTEMI and OCS-NSTEMI and cardiovascular death than non-cardiovascular death. The cardiac death rate at 1 year was 10.23% in patients with NOCS-NSTEMI vs. 5.86 % in OCS-NSTEMI (P<0.01) (Figure 2B). The incidence of readmission for MI through 12 months was distributed in a fashion similar to that of mortality rates across the 2 groups (Figure 2C). Following discharge from hospital, 6.1% of patients with OCS-NSTEMI and 13.1% with NOCS-NSTEMI were re-hospitalized for coronary diseases (P<0.01). The incidence of readmission for heart failure at 12-months was highest in the NOCS group (9.6%), compared to OCS group (5.6%) (P<0.01) (Figure 2D). The incidence of readmission for unstable angina at 12-months was highest in the NOCS group (14.2%), compared to OCS group (6.6%) (P<0.01) (Figure 2E). The outcomes were also analyzed with Cox regression analysis by covariates statistically different among the groups. After the adjustments for age, BMI, diabetes duration, smoking status, heart rate, troponin levels, cholesterol levels and LDL-cholesterol levels at baseline as well as dual anti-aggregant therapy at follow-up. NOCS-NSTEMI patients have a 3.6-fold higher risk of all death (P=0.010) (Figure 3A), a 3.3-fold higher risk of cardiac death (P=0.035) (Figure 3B), a 4.04- fold higher risk of re-admission for MI (P=0.013) (Figure 3C), and a 7.14-fold higher risk of re-admission for unstable angina (P<0.001) (Figure 3E) than OCS-NSTEMI patients. However, after risks adjustment, there was no increased risk of heart failure in NOCS-NSTEMI compared to OCS-STEMI patients (P=0.242) (Figure 3D). After 1-year follow-up, 6.8% of patients with obstructive PCI-treated lesions and 10.7% of patients with non-obstructive lesions evidenced an ejection fraction <40% (P<0.01). Similarly, 12 months after the event myocardial perfusion computed tomography evidenced a myocardial ischemia in 12.3% of patients with obstructive PCI-treated lesions and 20.5% of patients with non-obstructive lesions (P<0.01). Multiple logistic regression analysis demonstrated that ejection fraction <40%, at 12-months follow-up, was associated with non-obstructive non-PCI-treated lesions (P=0.034) as well as basal levels of cholesterol (P=0.02), LDL-cholesterol

(P=0.03), and triglycerides (P=0.019), whereas other confounders (age, body mass index, diabetes duration, smoking status and troponin levels) were again not significant. Finally, multiple logistic regression analysis demonstrated that myocardial perfusion defects, at 12-months follow-up, was associated with non-obstructive non-PCI-treated lesions (P=0.001) as well as age (P=0.042), BMI (P=0.03), smoking status (p<0.044) and troponin levels (P=0.022), whereas other confounders (cholesterol, LDL-cholesterol, triglycerides, and diabetes duration) were again not significant.

Figure legends

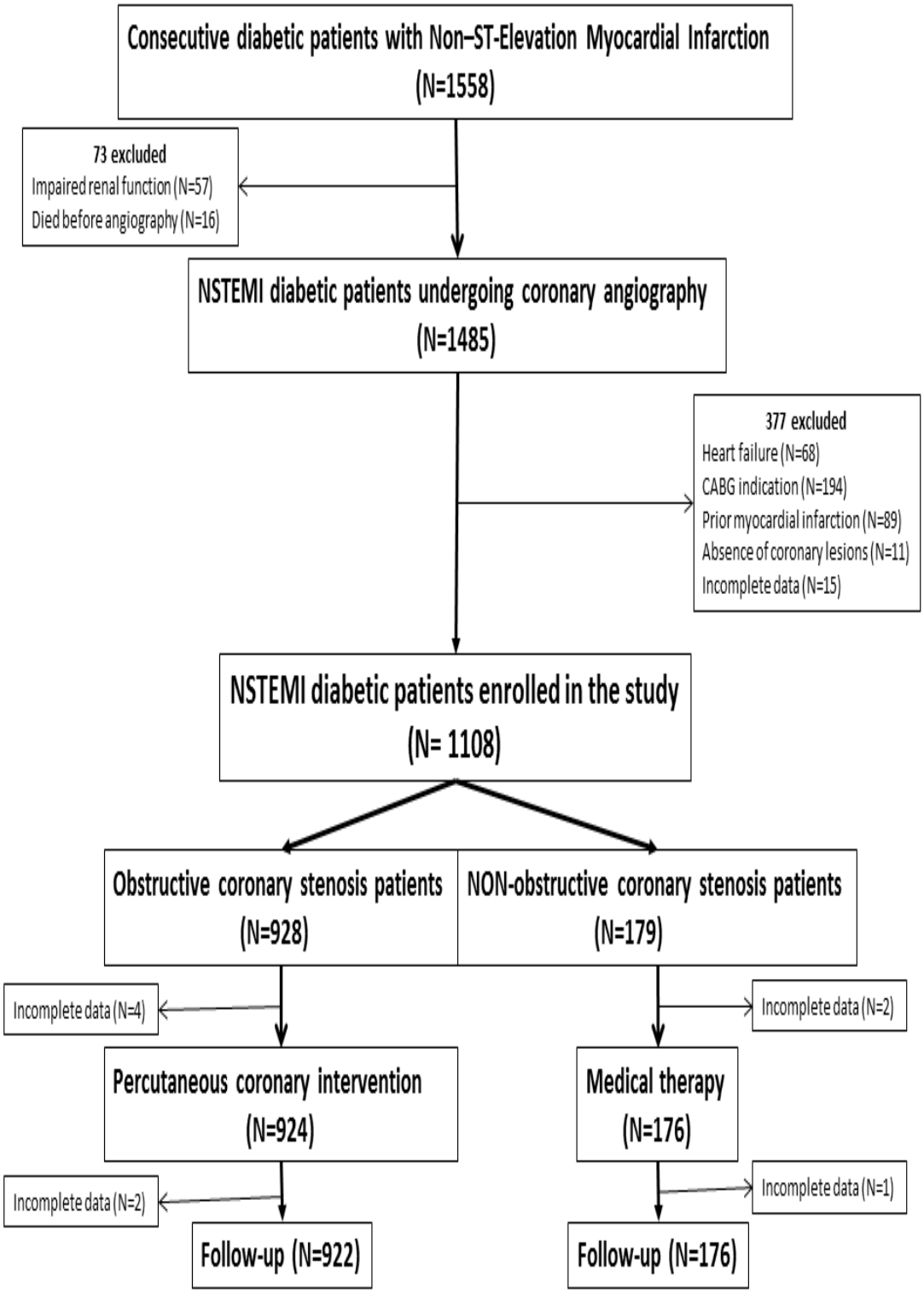

Figure 1: Flow diagram of study population.

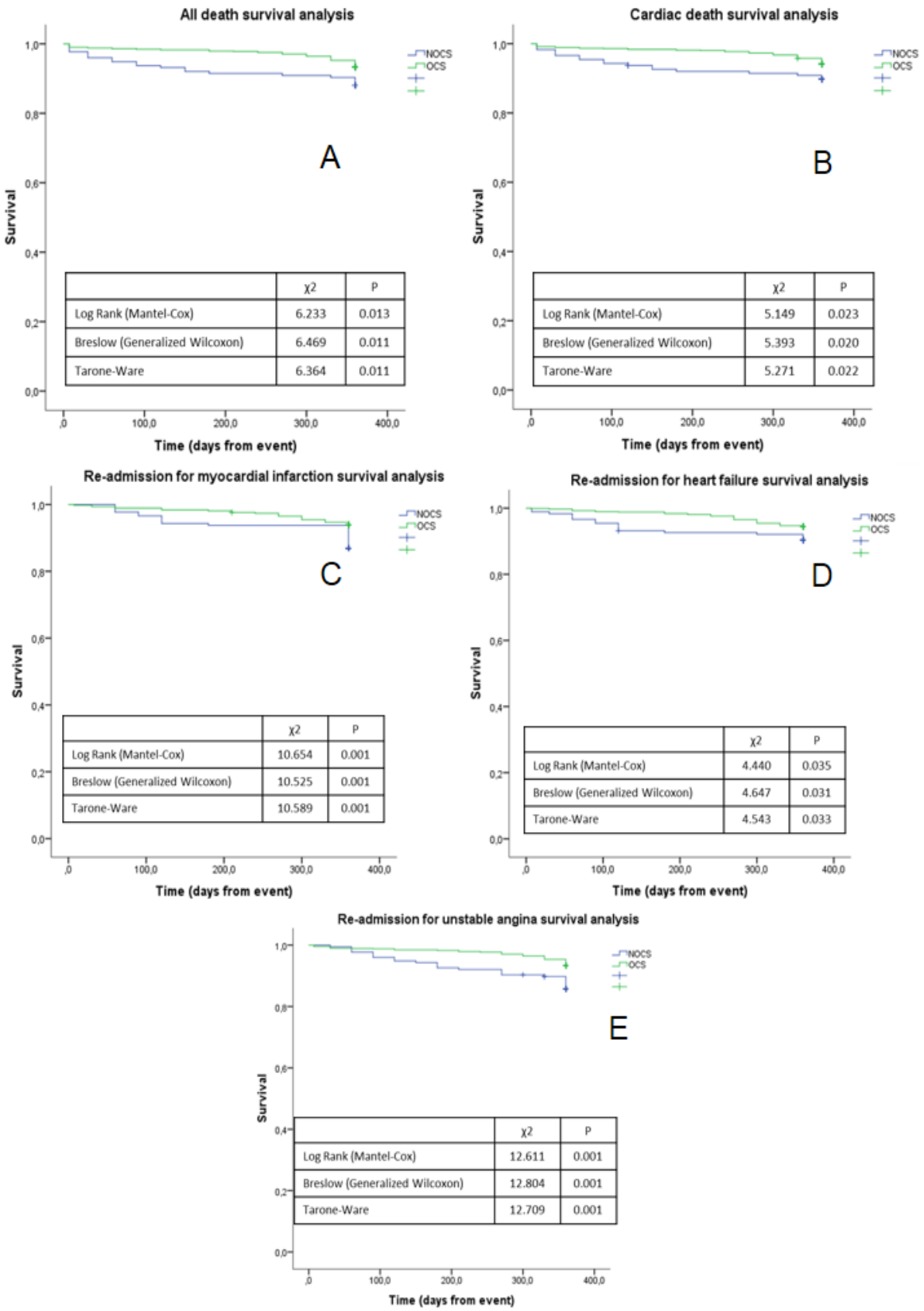

Figure 2: Kaplan–Meier curves showing cumulative incidence of readmission and mortality from 1 year after hospital discharge stratified by obstructive coronary stenosis (OCS) and non-obstructive coronary stenosis patients (NOCS).

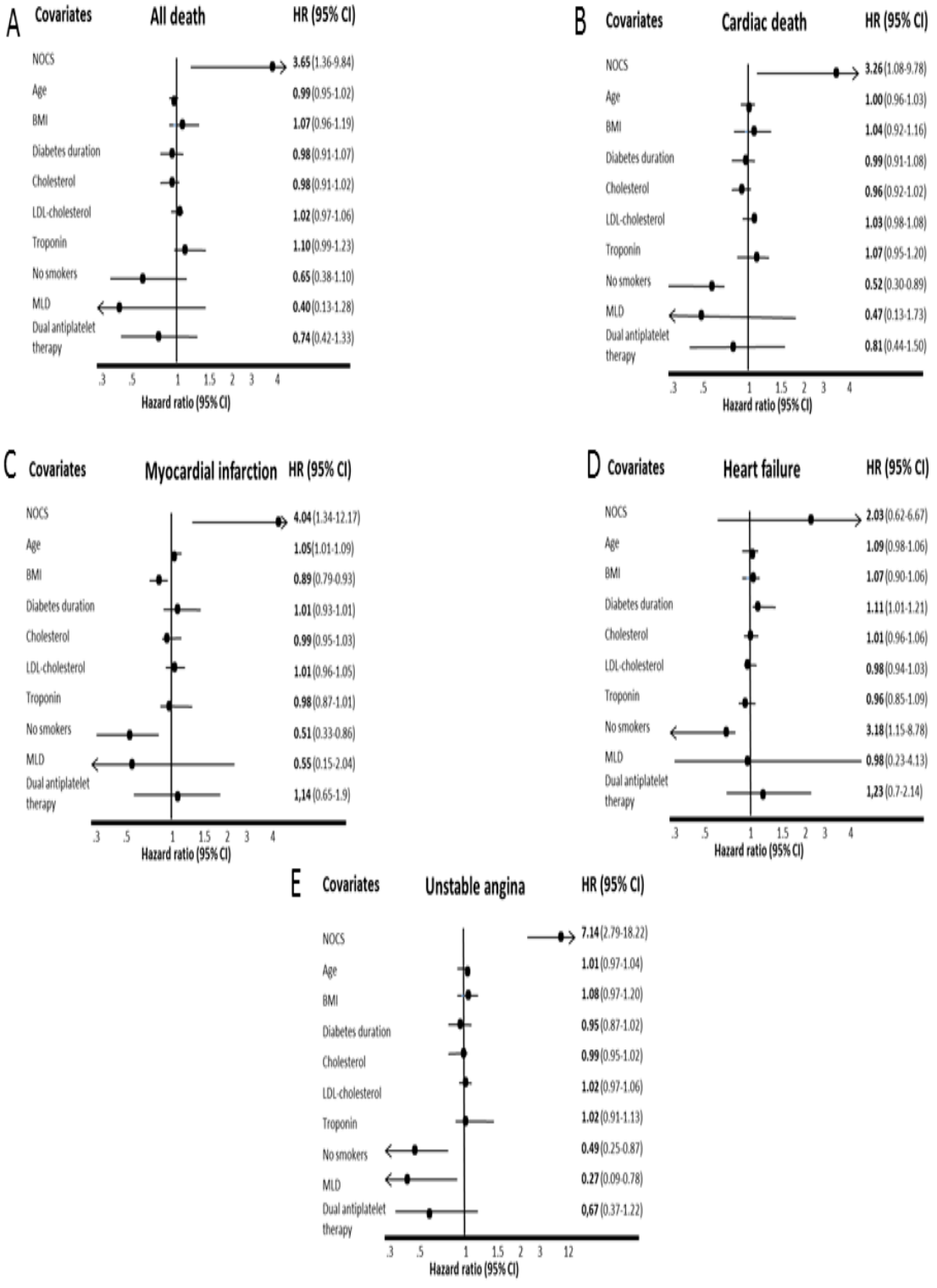

Figure 3: Hazard ratios (HR) and associated 95% confidence intervals are shown for all death (panel A), cardiac death (panel B), re-admission for myocardial Infarction (panel C), heart failure (panel D) and unstable angina (panel E) adjusted for age, BMI, diabetes duration, smoking status, heart rate, troponin levels, cholesterol levels, and LDL-cholesterol levels at baseline, and dual antiplatelet therapy at follow-up. The black circle indicates HR, and horizontal lines indicate 95% confidence intervals. NOCS, non-obstructive coronary stenosis patients; MLD: minimum luminal diameter.

Table 1: Baseline clinical characteristics, angiographic and procedural data.

	OCS	**group**	**NOCS**	**group**
	At admission	Follow-up	At admission	Follow-up
N	922		176	
Mean age (years)	68.8± 6.3	/	65.3±5.9*	/
Sex (M/F)	510/412	/	97/79	/
BMI (kg/m^2)	29.1±2.1	26.9±2.1ǂ	28.5±1.8*	26.8±1.8ǂ
Diabetes duration (years)	15.1±2.9	/	14.4±3.2*	/
Systolic blood pressure (mmHg)	126.9±12.3	123.5±12.2ǂ	126.5±12.9	123.4±12.9ǂ
Diastolic blood pressure (mmHg)	78.9±6.7	76.4±6.7ǂ	78.9±6.5	75.9±6.5ǂ
Heart rate (bpm)	87.7±8.6	76.7±8.7ǂ	87.1±7.9	74.1±8.1*ǂ
Killip class, n (%)				
I	601 (65.2)	/	115 (65.3)	/
II	156 (16.9)	/	38 (21.6)	/
III	165 (17.9)	/	23 (13.1)	/
GRACE score, n (%)				
Low	581 (63.0)		111 (63.1)	
Intermediate	166 (18.0)		35 (19.9)	
High	175 (19.9)		30 (17.0)	
ECG characteristics, n (%)				
Left bundle branch block	55 (5.9)	/	17 (9.7)	/
Q-wave	117 (12.6)	/	19 (10.8)	/
ST-depression	461 (50)	/	88 (50)	/
T-wave inversion	476 (51.6)	/	89 (50.6)	/
Risk Factors				
Stable angina, n (%)	156 (16.9)	/	30 (17)	/
Unstable angina, n (%)	110 (11.9)	/	21 (11.9)	/
Atrial fibrillation, n (%)	71 (7.7)	/	16 (9.1)	/
Stress hyperglycemia, n (%)	375 (40.6)	/	71 (40.3)	/
Hypertension , n (%)	437 (47.4)	/	83 (47.2)	/
Hyperlipemia, n (%)	203 (22.1)	/	39 (22.2)	/
Cigarette smoking, n (%)	156 (16.9)	/	19 (10.8)*	/
Active treatments				
β-blokers, n (%)	570 (61.8)	688 (74.6)ǂ	115 (65.3)	131 (74.4)ǂ
ACE inhibitors, n (%)	180 (19.5)	370 (40.1)ǂ	34 (19.3)	72 (40.9)ǂ
Angiotensin receptor blokers, n (%)	291 (31.6)	296 (32.1)	57 (32.4)	58 (32.9)
Calcium inhibitor, n (%)	156 (16.9)	175 (18.9)ǂ	24 (16.5)	32 (18.2)ǂ
Nitrate, n (%)	486 (52.7)	564 (61.2)ǂ	93 (52.8)	108 (61.2)ǂ
Statins, n (%)	430 (46.6)	700 (75.9)ǂ	81 (46)	132 (61.4)ǂ
Thiazide diuretic, n (%)	62 (6.7)	81 (8.8)ǂ	16 (9.1)	16 (9.1)
Insulin, n (%)	305 (33.1)	372 (40.3)ǂ	59 (33.5)	72 (40.1)ǂ
Oral antidiabetic, n (%)	712 (77.2)	719 (77.9)	136 (77.3)	136 (77.3)
Aspirin, n (%)	518 (56.2)	868 (94.1)ǂ	99 (56.2)	165 (93.7)ǂ
Thienopyridine, n (%)	131 (14.2)	788 (85.5)ǂ	25 (14.2)	133 (75.6)*ǂ
Dual anti-aggregant therapy	/	755 (81.9)	/	123 (69.9)*
Low-molecular heparin, n (%)	64 (6.9)	100 (10.8)ǂ	12 (6.8)	19 (10.8)ǂ
Vitamin-K antagonist, n (%)	31 (3.4)	36 (3.9)ǂ	6 (3.4)	6 (3.4)
Laboratory analyses				
Plasma glucose (mg/dl)	200.1 ± 286	179.3±27.3ǂ	201.2 ± 24.7	178.9±25.7ǂ
HbA1c (%)	8.4 ± 1.5	7.4±1.5ǂ	8.4 ± 0.7	7.3±0.9ǂ
Cholesterol (mg/dl)	202.7 ± 22.1	192.4±23.4ǂ	197.7 ± 21.1*	192.4±21.1ǂ
LDL-cholesterol (mg/dl)	127.9 ± 21.4	119.5±22.7ǂ	124.1 ± 20.7*	119.7±20.9ǂ
HDL-cholesterol (mg/dl)	37.9 ± 3.5	40.7±3.8ǂ	37.3 ± 3.4	40.2±3.6ǂ
Triglycerides (mg/dl)	184.6 ± 21.9	160.6±22.1ǂ	181.8 ± 19.6	162.8±19.6ǂ
Creatinine (mg/dl)	0.99 ± 0.15	1.0±0.1	0.99 ± 0.15	1.0±0.2
hs-cTnT (ng/l)	149.9 ± 17.7	/	144.8±33.2*	/
LVEF, n (%)				
>50%	483 (52.4)	538 (58.3)ǂ	91 (51.7)	95 (54.1)ǂ

	OCS	group	NOCS	group
41% to 50%	367 (39.8)	321 (34.8)ǂ	70 (39.7)	62 (35.2)ǂ
25% to 40%	72 (7.8)	63 (6.8)ǂ	14 (7.9)	19 (10.7)*ǂ
Procedural data				
Symptom onset to angiography, h	7.1 ± 2.1	/	6.9 ± 0.77	/
Insulin infusion time, min	39.3 ± 5.1	/	38.7 ± 2.9	/
Angiographic data				
Stenosis severity, %				
Non-obstructive lesions <50%, n	104	/	311	/
Obstructive lesions ≥50%, n (%)	1614	/	/	/
<25%	26 (1.5)	/	50 (16,1)	/
26-49%	78 (4.5)	/	261 (93.9)	/
50-69%	988 (57.6)	/	/	/
70-99%	609 (35.4)	/	/	/
100%	17 (1.0)	/	/	/
Lesion location, n (%)				
LAD	773 (45)	/	140 (45)	/
LCx	533 (31)	/	93 (30)	/
RCA	344 (20)	/	63 (20)	/
LM	68 (4)	/	15 (5)	/
Number of diseased vessels, n (%)				
1-VD	223 (24.2)	/	45 (25.6)	/
2-VD	596 (64.6)	/	127 (72.1)	/
3-VD	101 (10.9)	/	4 (2.3)	/
Quantitative angiographic data				
Lesion lenght, mm	20.5 ± 2.1	/	14.8 ± 5.1*	/
Reference diameter, mm	2.8 ± 0.2	/	2.7 ± 0.4	/
MLD, mm	1.07 ± 0.17	/	1.79 ± 0.16*	/
Myocardial scintigraphy SDS>3	/	113 (12.3)	/	65 (20.5)*

Data are means ± SD or n (%). 1-VD indicates single-vessel disease; 2-VD, two-vessel disease; 3-VD, three-vessel disease; LAD, left anterior descending; LCx, left circumflex artery; RCA, right coronary artery; LM, left main; MLD, minimum luminal diameter; SDS, Summed Difference Score. *P<0.05 vs OCS group. ǂP<0.05 vs At admission.

DISCUSSION

The present study compared the 1-year outcomes of "real world" unselected type 2 diabetic patients with NOCS-NSTEMI versus type 2 diabetic patients with OCS-NESTEMI who had undergone coronary angiographic study in the acute phase of the event. The main results were as follows: first, the rate of NOCS-NSTEMI during coronary angiography (16%) was not negligible; second, in a contemporary sample of type 2 diabetic patients with NOCS-NSTEMI treated with medical therapy in routine practice, we observed higher cumulative incidence of 1-year mortality and adverse cardiovascular outcomes, compared to type 2 diabetic patients with OCS-NSTEMI treated with revascularization strategy in routine practice; third, the 1-year prognosis of type 2 diabetic patients with NOCS-NSTEMI was not event free, with a 36.9% rate of re-admission for cardiovascular diseases at a mean follow-up of 12 months. Finally, the type 2 diabetic patients with NOCS-NSTEMI were often undertreated with cardio-protective medications, including dual oral antiplatelet therapy.

The prognosis of patients with NOCS-NSTEMI has been evaluated, by a recent study[15], which evidenced higher risk for all-cause mortality and reduced risk for cardiac mortality and MI compared with matched patients with obstructive CAD. However, this study did not provide any evidence about the influence of NOCS-NSTEMI management on outcomes following the cardiac event, in diabetic patients. Previous studies[16-18] evaluated the influence of diabetes as well as the different treatment strategies on mortality following acute coronary syndrome (ACS). However, these studies did not provide any evidence about the influence of NOCS-NSTEMI management on outcomes following the cardiac event, in diabetic patients. In this context, a recent study[19] assessed the association between non-obstructive CAD and 1-year hospitalization for nonfatal MI and all-cause mortality rates without MI at baseline in patients underwent elective coronary angiography for positive functional study, chest pain and stable angina. Among 37.674 patients in the study cohort, 15.699 (41.7%) had diabetes, and 1-year mortality outcome rates were significantly higher in OCS than in NOCS patients. However, because about 44% of OCS patients of Maddox study[19] had not been treated with PCI or CABG, these data are not comparable with our results. In our DIA-MYCONOS study after NSTEMI, the 1-year follow-up results show a 5.2% reduction in the primary endpoint of all death and 4.3% of cardiac death by an early invasive strategy in OCS-NSTEMI compared with a noninvasive strategy in NOCS-NESTEMI despite a

lower severity of atherosclerotic disease (coronary stenosis <50%) at baseline. Obviously, the baseline angiographic characteristics of coronary stenosis treated by revascularization strategy were significantly different from the coronary stenosis treated with medical strategy, as evidenced by higher number of diseased vessels and higher lesion lengths. Nevertheless, 1-year risk of adverse outcomes was highest among NOCS-NSTEMI treated with a medical management strategy without revascularization and lowest among OCS-NSTEMI who underwent PCI. Moreover, our data indicate an increased incidence of cardiovascular disease in NOCS-NSTEMI patients, both after adjustment for demographic variables (age, BMI and diabetes duration) and after further adjustment for other cardiovascular risk factors (smoking, total cholesterol, LDL-cholesterol, and troponin levels). The number of diabetic subjects in this report was large and the samples of subjects with OCS-NSTEMI and NOCS-NSTEMI were population-based, suggesting that these results may be generalizable. This difference in event rate was based on a continued difference in rates of death, which had risen from 1.11% to 11.9% in NOCS-NSTEMI and from 1.14% to 6.72% in OCS-NSTEMI after 1 year. In this context, the poor outcomes of NOCS-NSTEMI compared to OCS-NSTEMI PCI-treated, observed in our study, might be explained by a more slow progression of coronary atherosclerosis extension in obstructive coronary diseases as result of PCI, compared to an abruptly increment of atherosclerosis in non-obstructive coronary diseases treated with medical management strategy alone.

Our analysis has several limitations. We evaluated the groups of patients with diabetes that were not well matched at baseline. Moreover, the management of therapy during the follow-up has been different among the groups. However, the regression analysis may be reduced the study bias. These findings demonstrate the 1-year risk for patients with NOCS-NSTEMI treated with a medical management strategy in routine practice, provide a benchmark for event rate considerations for future studies evaluating long-term therapies in type 2 diabetic post-MI population. Given the increasing burden of cardiovascular disease attributable to diabetes worldwide, our study highlights the need for a major research effort to identify aggressive new strategies to manage unstable ischemic heart disease among this high-risk population.

CONCLUSIONS

These findings, consistent with prior biologic studies indicating that a majority of MIs are related to non-obstructive stenosis[20-25], highlight the need to recognize that non-obstructive coronary stenosis is associated with significantly increased risk for death and MI in diabetic people after NSTEMI. Correspondingly, these results reveal the limitations of a dichotomous characterization of angiographic CAD into “obstructive” and “non-obstructive” to predict death and MI and suggest the importance of preventive strategies such as pharmacotherapy treatments and lifestyle modifications to mitigate these risks. Moreover, the recognition that ruptured plaque, rather than occlusive plaque, is the genesis for most death and MIs[24, 25], along with the recognition that the majority of ruptured plaques arise from non-obstructive stenosis[26], suggests that non-obstructive CAD is associated with significant risk for MI and all-cause mortality and provided the rationale for this investigation.[27, 28] In this scenario, the diabetic status may affects several pathogenetic mechanisms that favor the plaque instability and subsequently plaque rupture in the absence of obstructive CAD, including inflammation, endothelial dysfunction with the inability to augment coronary flow in response to stress and vasospasm.[29-33] Finally, the unfavorable outcome might, in part, be explained by the lower rate of the prescription of dual antiplatelet drugs in patients with non-obstructive CAD, consistent with the findings from previous studies.[34] These patients are often undertreated in the belief that NOCS-NSTEMI represents a benign condition. Moreover, premature discontinuation of aspirin and/or thienopyridine was significantly more frequent among patients with non-obstructive CAD than among those with critical CAD, which might have contributed to the greater incidence of adverse events in NOCS-NSTEMI.

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