Effect of Diabetes Mellitus and Left Ventricular Perfusion on Frequency of Development of Heart Failure and/or All-cause Mortality Late After Acute Myocardial Infarction

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Type 2 diabetes mellitus (DM) has a detrimental impact on cardiovascular outcomes, with implications for prognosis following ST elevation myocardial infarction (STEMI).The aim was to evaluate the impact of DM and myocardial perfusion on the long-term risk of heart failure (HF) and/or all-cause mortality following primary percutaneous coronary intervention (pPCI) for STEMI. A total of 406 STEMI patients (104 with DM) treated with pPCI were enrolled in this observational study. Myocardial perfusion was reassessed with the Quantitative Myocardial Blush Evaluator. Follow-up data on HF (ICD10 [International Statistical Classification of Diseases] codes I50.0 − I50.9) and all-cause mortality were obtained from the National Health Fund. During a 6-year follow-up, 36 (35%) patients with DM died compared with 45 (15%) patients without DM (p <0.001). Also, 24 (23%) patients with DM developed HF compared with 51 (17%) patients without DM (p = 0.20). Patients with DM and HF had the highest mortality rate (75%), and those with DM and a QuBE score below the median value (9.0 arb. units) had significantly higher risk of HF (hazard ratio [HR] =1.96, 95% CI 1.18 to 3.27, p = 0.0099) and the composite of HF and/or all-cause mortality (HR = 1.89, 95% CI 1.33 to 2.69, p = 0.0004). In conclusion DM (type 2) and diminished myocardial perfusion increase the risk of HF and/or all-cause mortality during a 6-year follow-up after pPCI for STEMI. **(Am J Cardiol 2021;140:25−32)**

The global burden of type 2 diabetes mellitus (DM) is rising dramatically, and according to the International Diabetes Federation, the morbidity and mortality associated with DM will increase further.[1] HF is another global public health problem,[2] being a significant issue among patients with DM.[3] It is estimated that 40 % of hospitalized patients with HF with reduced ejection fraction (EF) have DM.[4] The etiology of HF encompasses many different conditions, yet coronary heart disease, and acute myocardial infarction (AMI) are considered among the most frequent underlying causes.[5] The recommended treatment of acute ST elevation myocardial infarction (STEMI) is timely performed primary percutaneous coronary intervention (pPCI), restoring flow in the culprit artery.[6] However, diabetic patients are more likely to have impaired myocardial perfusion following pPCI when compared with patients with normal glucose tolerance.[7] The objective of this study is to evaluate the impact of DM and myocardial perfusion on the long-term risk of HF and/or all-cause mortality following pPCI for STEMI.

Methods

This was a single center, retrospective, cohort study where we have reviewed the medical records of consecutive patients admitted to a cardiology ward due to STEMI between January 2004 and December 2014. The diagnosis of STEMI was based on universal definition of AMI.[8] The eligibility criteria were as follows: consecutive patients of age ≥ 18 years with STEMI, complete hospital medical records, good quality electrocardiographic tracings and angiograms, the absence of HF before the hospital admission. Exclusion criteria were coronary artery lesions not amenable to stent implantation or balloon angioplasty, chronic total coronary occlusion which could not be revascularized or referral of the patient for bypass surgery.

Patients were considered to have DM based on a known history of DM at admission (preexisting DM). All of the patients were treated with pPCI as recommended by the respective guidelines. The administration of glycoprotein IIB/IIIA inhibitors, as well as the use of aspiration catheters, was at the operator's discretion. We recorded demographic, clinical, procedural, and laboratory data. Anthropometric parameters, namely, height (cm) and weight (kg), were measured by standard methods, and the

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body mass index was calculated as weight/height^2 (kg/m^2) on the day of hospital discharge. Blood pressure was measured as a routine in-hospital procedure at least twice a day and recorded in patients' medical histories. A median value of all in-hospital measurements was recorded. Arterial hypertension was defined as a systolic blood pressure $\geq$ 140 mm Hg and/or a diastolic blood pressure $\geq$ 90 mm Hg or treatment with antihypertensive medications.

Every patient signed an informed consent agreement for in-hospital treatment on admission. No additional consent was obtained before the retrospective analysis of these anonymized registry data.

Detailed description of angiographic reanalysis, noninvasive assessment of myocardial perfusion, assessment of infarct size, and echocardiographic measurements were reported previously.[9] For the operator-independent evaluation of myocardial perfusion, we used the on-line software, Quantitative Blush Evaluator available at http://www.stellarjackpot.com/qube/.[10]

Hemoglobin A1c was determined using a high-performance liquid chromatography method, and the results were expressed in the National Glycohemoglobin Standardization Program/Diabetes Control and Complications trial units. Fasting plasma glucose was determined by the enzymatic method. Cholesterol and triglycerides were measured using enzymatic methods, with high-density lipoprotein cholesterol measured after precipitation of very low-density lipoprotein. The concentration of low density lipoprotein cholesterol was calculated using the Friedewald formula. Serum creatinine was measured by means of Jaffe's method. The estimated glomerular filtration rate per 1.73 m^2 was calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula.[11]

The primary end point of the study was the all-cause mortality. Secondary end points were the new onset of HF or a combined end point of the new onset HF and/or all-cause mortality during the 6-year clinical follow-up after STEMI.

To assess the new onset HF the electronic medical records database of eligible patients was obtained from the National Health Fund (NHF) and updated for the 6-year clinical follow-up after STEMI and the incidence of HF was recorded. International Classification of Diseases, 10th revision (ICD-10) codes I50.0 − I50.9 reported to NHF at the time of the patient's discharge or during the 6 years of follow-up were considered as development of HF.[12] The diagnosis of in-hospital new onset of HF was based on European Society of Cardiology recommendations.[13]

Our focus was on clinical presentations with HF, and have not discriminated HF into subtypes of HF with preserved, mildly reduced, or reduced EF.[13] To assess the all-cause mortality, data at follow-up were derived from the General Electronic Population Death Registry System in Poland. Follow-up began on the date of STEMI and continued until the date all-cause death or until 6 years after STEMI.

The Kolmogorow-Smirnov test was used to assess normality and Levene's test was used to test for the homogeneity of variances. Quantitative data are presented as the mean (standard deviation) or median with interquartile range (Q1-Q3) for data that did not have normal distribution. Categorical data are presented as numbers and percentages. The variables which were distributed not normally were analyzed using non-parametric Mann-Whitney *U* test for pairwise, and Kruskal-Wallis test for multiple comparisons, respectively. Two-tailed ANOVA (analysis of variance), Kruskal-Wallis, and chi-square tests were used for multiple comparisons of continuous, continuous with not normal distribution, ordered or categorical variables, respectively. Chi-square test with Yates correction was used, and it was corrected for multiple comparisons. Any statistical significance in the ANOVA was confirmed with Student's *t* test with Bonferroni correction for multiple comparisons. Any statistical significance in the Kruskal-Wallis analysis was confirmed with chi-square with Yates correction for pairwise comparisons. The Kaplan-Meier test was used to compare event-free survival between groups during follow-up.

Multivariate Cox proportional hazard modeling was used to find predictors of adverse outcomes. Additionally, multivariate Cox proportional hazard analysis of mortality was performed using LVEF for stratification. We have applied a forward stepwise approach with all demographic, clinical, angiographic, and procedural variables (with p = 0.15 to exclude). We have sub-analyzed crude data and after their adjustment for age and gender, as well as we have additionally analyzed the entire study population and a subpopulation of diabetic patients. Adjustment for age and gender yielded negligible differences, so we have used the crude, unadjusted data for Cox analysis. Furthermore, crude data are presented in the tables.

A 2-tailed p value < 0.05 was considered to be significant. Statistica 12 (Statsoft Inc., Tulsa, Oklahoma), equipped with the Medical Package (Statsoft Polska, Kraków, Poland) was used for data analysis.

Results

We identified 773 patients with complete medical data fulfilling the study inclusion/exclusion criteria. Of these 406 patients (104 patients with DM) met the inclusion criteria with no exclusion criteria and were selected for further analysis and up to a 6-year-long follow-up. Distribution of ineligibility criteria was comparable between diabetic and non-diabetic patients who were not enrolled into the study.

Table 1, Table S1, and Table S3 summarize the study population characteristics stratified according to DM, HF, and combination of HF/all-cause death status. Regarding DM, only the information concerning the duration of the disease was recorded. As expected, the DM population had substantially different demographic and clinical presentation in comparison to the non-DM patients, with older mean age and higher number of comorbidities (Table 1). In the subgroup of DM patients with new onset HF (Table S1) or who had new onset HF and/or death (Table S3) during the follow-up, the oldest age and lowest renal glomerular filtration was evident.

Patients with DM had a significantly worse procedural outcome: epicardial flow in the infarct-related artery was slower (higher number of corrected TIMI frame count cTFC), and myocardial perfusion was impaired (lower QuBE score), as well as a larger enzymatic infarct size and significantly impaired left ventricular function (lower left

Table 1
Demographics, baseline characteristics of study patients

Variable	Diabetes mellitus		p (t, U M-W or Chi^2 tests)
	YES (n = 104)	NO (n = 302)	
Men	54 (52%)	219 (76%)	<0.001
Age (years) mean (SD)	66.7 (9.5)	60.5 (10.9)	<0.001
Hypertension	91 (88%)	179 (60%)	<0.001
Hyperlipidemia	59 (56%)	176 (58%)	0.86
Smoker	37 (36%)	183 (61%)	<0.001
Family history of CHD	34 (33%)	107 (35%)	0.69
Previous MI	22 (21%)	47 (16%)	0.59
Previous PCI	26 (25%)	43 (14%)	0.02
Previous CABG	5 (5%)	6 (2%)	0.54
Weight (kg) mean (SD)	81.9 (11.3)	79.5 (13.3)	0.72
Height (m) mean (SD)	1.7 (0.0)	1.7 (0.1)	0.94
Body mass index (kg/m^2) mean (SD)	29.0 (3.9)	27.6 (3.9)	0.002
Symptom duration (min) median (Q1;Q3)	354 (180;463)	300 (150;360)	0.22
Killip class			
I	95 (91%)	275 (91%)	0.85
II – IV	9 (9%)	27 (9%)	
Creatinine (μmol/L) mean (SD)	83.1 (29.9)	81.8 (55.6)	0.75
eGFR* (ml/min/1.73m^2) mean (SD)	82.4 (25.3)	92.5 (25.2)	<0.001
Fasting plasma glucose (mg/dL) mean (SD)	150.6 (80.6)	94(10.1)	0.001
HbA1c (%) mean (SD), (mmol/mol) mean (SD)	7.9 (2.5) (62.8 (19.6))		
Drugs at discharge			
Acetyl salicylic acid	104 (100%)	302 (100%)	0.97
Clopidogrel	103 (99%)	294 (97%)	0.86
Beta-blocker	100 (96%)	285 (94%)	0.98
Ca-channel blocker	21 (20%)	55 (18%)	0.66
ACE inhibitors/ARB	102 (98%)	285 (94%)	0.89
Statin	97 (93%)	286 (95%)	0.88
Diuretics	38 (37%)	62 (21%)	0.002
MRA	15 (14%)	33 (11%)	0.47

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; Ca, calcium; CABG, coronary artery bypass graft surgery; CHD, coronary heart disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; MI, myocardial infarction; MRA, mineralocorticoid receptor agonist; PCI, percutaneous coronary intervention; U M-W, Mann-Whitney *U* test.

Drugs administered at discharge are outlined in the bottom lines.

* estimated glomerular filtration rate according to CKD-EPI formula, Conversion factors to SI units are as follows: for glucose, 0.05551. A p value of <0.05 is considered statistically significant.

ventricular EF) in the pre-discharge period (Table 1). Long-term follow-up data were available for all patients. Across the short (30 days), medium (1 year), and long-term (6 years) follow-up, DM patients had numerically higher incidence of the new-onset HF when compared with non-DM patients, although this did not reach statistical significance. Although analyzing all-cause death and a composite outcome, these were significantly more frequent in DM patients when compared with non-DM patients (Table 2).

When we adjudicated all-cause mortality at 6-years to DM and HF status, DM doubled the risk (HR = 1.88, 95% CI 1.11 to 3.19) and new onset HF almost tripled the risk (hazard ratio [HR] = 2.55, 95% confidence interval [CI] 1.57 to 4.14) of all-cause death. The mortality rate 6 years post-AMI was as high as 75% in DM patients in whom new onset HF had developed (Figure 1).

The QuBE score values were significantly lower in DM patients, in whom HF had developed, who have died or in whom a combined adverse event has occurred in the follow-up (Figure 2, Table S2 and Table S4).

Patients with DM and impaired myocardial perfusion (QuBE < 9 AU), had significantly lower event-free survival (Figure 3). These patients are at the highest risk of the development of new onset HF and had the highest risk of all-cause mortality.

Multivariate Cox proportional hazard analysis of all clinical variables (Table 3) shows that several demographic, clinical, and procedural factors were independent predictors of adverse outcomes. The quantitative myocardial blush evaluator score is an independent predictor of all-cause mortality (HR = 0.94, 95% CI 0.89 to 0.99) and combined end point in DM patients (HR = 0.96, 95% CI 0.92 to 0.99).

DM itself was the strongest (HR = 2.36, 95% CI 1.47 to 3.79) risk factor for all-cause mortality in the entire study population, whereas HF is the strongest (HR = 2.4, 95% CI 1.51 to 3.82) risk factor for all-cause mortality in the diabetic subpopulation. Adjustment for age and gender did not changed the results significantly. Use of LVEF as cofounder eliminated CK-MB at admission from the list of all-cause mortality predictors for entire study population.

Table 2
Adjudicated short-, mid- and long-term outcomes according to presence of diabetes mellitus

Variable		30 days	p	1 year	p	6 years	p
Heart failure	DM(+) (n = 104)	6 (6%)	0.06	17 (16%)	0.3	24 (23%)	0.20
	DM(-) (n = 302)	5 (2%)		37 (12%)		51 (17%)	
All-cause death	DM(+) (n = 104)	4 (4%)	0.06	13 (13%)	0.01	36 (35%)	<0.001
	DM(-) (n = 302)	2 (1%)		14 (5%)		45 (15%)	
Heart failure or all-cause death	DM(+) (n = 104)	9 (9%)	0.01	24 (23%)	0.1	42 (40%)	0.02
	DM(-) (n = 302)	7 (2%)		48 (16%)		81 (26%)	

Abbreviations: DM, diabetes mellitus.
A p value of <0.05 was considered statistically significant.

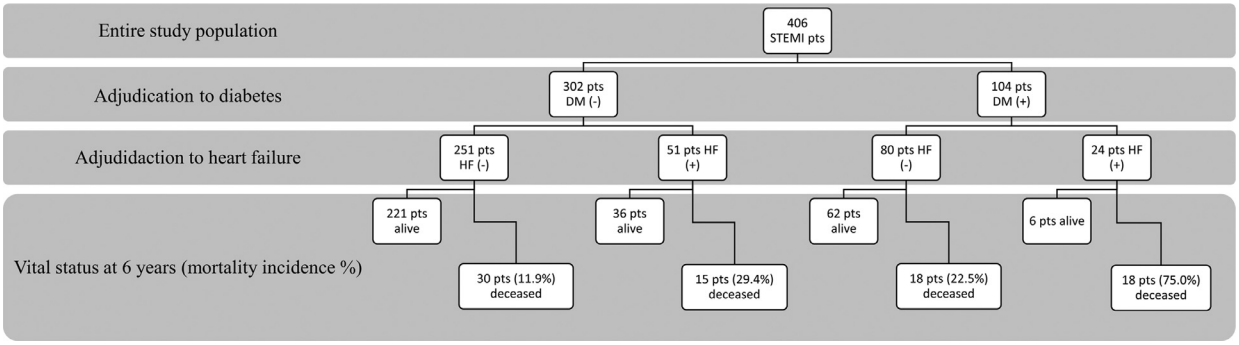

Figure 1. Incidence of all-cause mortality at 6 years adjudicated to type 2 diabetes and heart failure. Abbreviations: HF, heart failure; pts, patients; STEMI, ST elevation myocardial infarction; others, see Table 1.

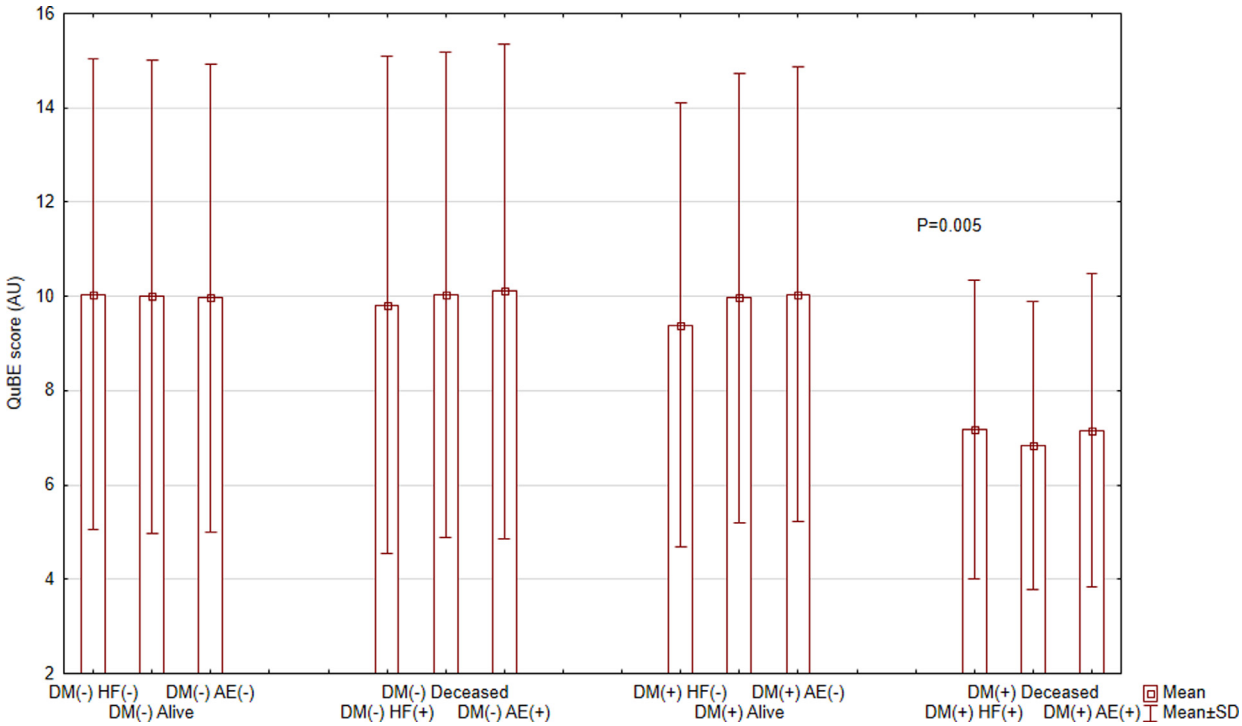

Figure 2. Myocardial perfusion with operator-independent Quantitative Blush Evaluator (QuBE). Abbreviations: see Table 1 and Table 3 and Figure 1.

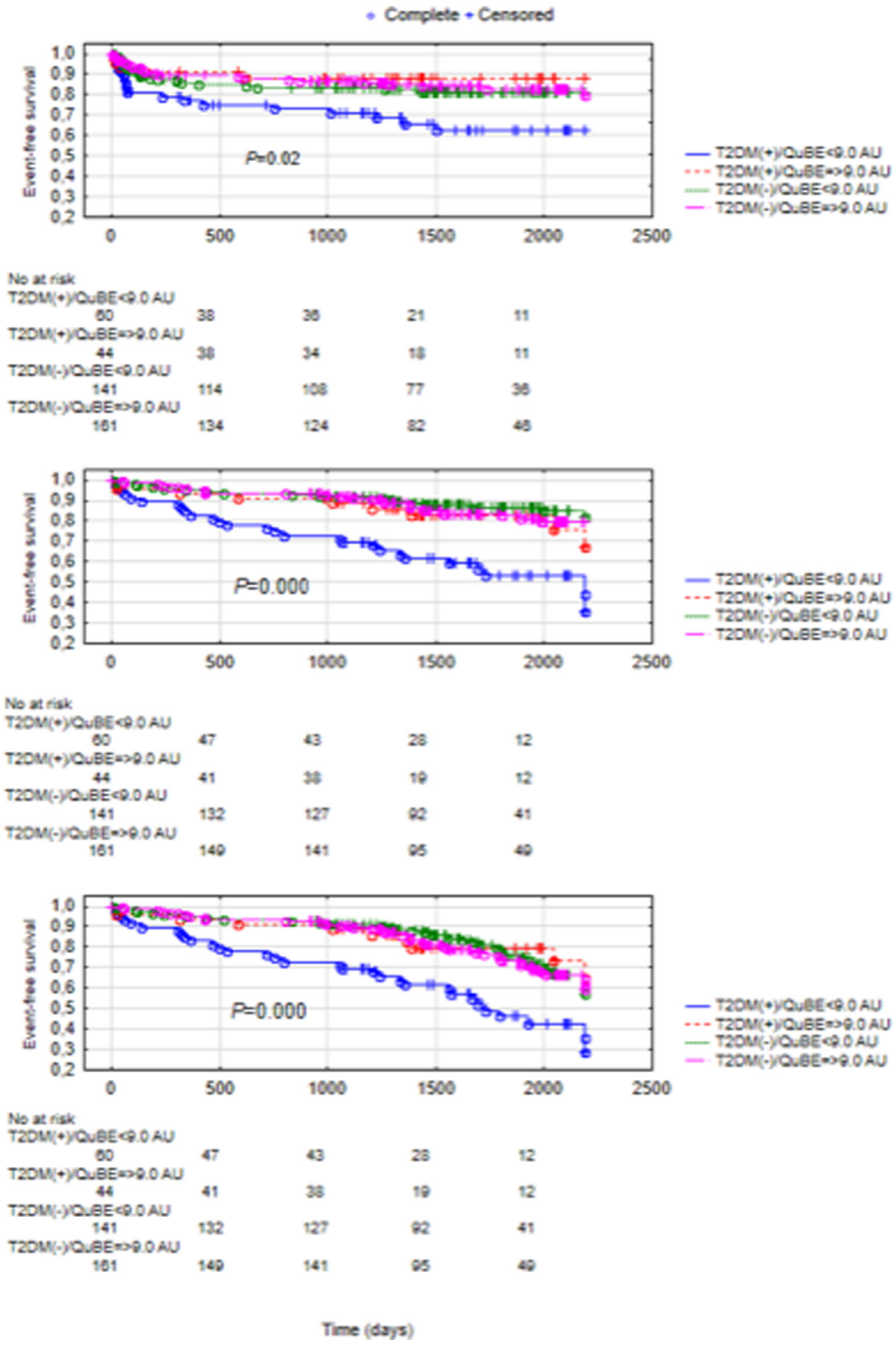

Figure 3. Kaplan-Meier curves of heart failure free (upper panel), all-cause mortality free (middle panel), and combined heart failure/all-cause mortality free (lower panel) survival. Groups are adjudicated to DM and myocardial perfusion assessed with QuBE – median value of QuBE score = 9AU is the cut-off. Abbreviations: see Table 1 and 3.

Discussion

The major findings of the present study are as follows: (1) despite a comparable distribution of epicardial flow and myocardial blush grade after pPCI among patients with and without DM, DM patients had significantly diminished myocardial perfusion assessed by an operator independent QuBE; and (2) DM patients and a QuBE score below the median value were at the highest risk of adverse outcomes in the long-term follow-up.

There are several methods for evaluating myocardial perfusion, though the reference methods, such as the evaluation of the coronary blood flow velocity,[14] myocardial

Table 3
Multivariate predictors of long-term adverse outcomes in entire study population and in subgroup of DM patients

	All patients (n = 406)		DM patients (n = 104)	
Long-term adverse outcomes	Predictor	HR (95% CI)	Predictor	HR (95% CI)
Heart failure	cTFC (1 fps increment)	1.01 (1.00−1.02)	cTFC (1 fps increment)	1.01 (1.00−1.02)
	Tp adm (1,000 ng/L increment)	1.10 (1.00−1.30)	Tp adm (1,000 ng/L increment)	1.21 (1.07−1.35)
	Tp 72 hours (1,000 ng/L increment)	1.40 (1.10−1.60)	Tp 72 hours (1,000 ng/L increment)	1.35 (1.08−1.63)
	LVEF (1 % increment)	0.95 (0.93−0.97)	LVEF (1 % increment)	0.95 (0.93−−0.97)
	Male gender	0.56 (0.35−0.90)	Male gender	0.62 (0.39−0.99)
			eGFR (1 ml/min/m^2 increment)	0.99 (0.98−1.00)
All-cause death	Age (1 year increment)	1.07 (1.05−1.10)	Age (1 year increment)	1.07 (1.05−1.10)
	CK-MB adm (100 u. increment)	1.30 (1.03−1.41)	Tp 72 hours (1,000 ng/L increment)	1.41 (1.18−1.63)
	Tp 72 hours (1000ng/L increment)	1.33 (1.08−1.58)	LVEF (1 % increment)	0.96 (0.94−0.98)
	LVEF (1 % increment)	0.96 (0.94−0.98)	QuBE (1 unit increment)	0.94 (0.89−0.99)
	DM	2.36 (1.47−3.79)	Heart failure	2.40 (1.51−3.82)
	Hypertension	0.50 (0.31−0.82)		
	Heart failure	2.25 (1.40−3.62)		
Heart failure and/or all-cause death	Age (1 year increment)	1.04 (1.02−1.06)	Age (1 year increment)	1.05 (1.03−1.07)
	cTFC (1 fps increment)	1.01 (1.00−1.01)	Tp adm (1,000 ng/L increment)	1.14 (1.02−1.26)
	Tp 72 hours (1,000ng/L increment)	1.43 (1.21−1.65)	Tp 72 hours (1,000 ng/L increment)	1.42 (1.20−1.63)
	LVEF (1 % increment)	0.95 (0.93−0.97)	LVEF (1 % increment)	0.95 (0.94−0.97)
	DM	1.50 (1.02−2.21)	QuBE (1 unit increment)	0.96 (0.92−0.99)

Abbreviations: adm, admission; CK-MB, muscle-brain creatine kinase isoenzyme; cTFC, corrected Thrombolysis in Myocardial Infarction frame count; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; fps, frame per second; HR, hazard ratio; LVEF, left ventricle ejection fraction; QuBE, quantitative myocardial blush evaluator; Tp, troponin.

contrast echocardiography,[15] or magnetic resonance imaging,[16] are not widely used for prognostic purposes in post-infarction patients due to complexity, cost or limited access to these methods. The QuBE software was designed to facilitate an operator-independent assessment of myocardial perfusion and correlates with other measures of infarct size and myocardial perfusion.[10] The visual scales for myocardial perfusion assessment provide inconsistent results. Researchers from HORIZONS AMI trial assessed myocardial perfusion using the Tissue Myocardial Perfusion Grade and reported that diabetic patients had significantly higher mortality, although there was no correlation between DM and myocardial perfusion.[17] MBG and STR (ST -segment resolution) substudies of the CADILLAC trial utilized the alternative visual scale−−MBG and another measure, based on STR in electrocardiography, to assess myocardial perfusion.[18] In the latter study, a significantly higher percentage of patients with DM had impaired myocardial perfusion, as assessed by lower values of MBG and a higher rate of incomplete STR when compared with non-diabetic patients.

Although Araszkiewicz et al.[19] reported an almost 60% incidence in signs and symptoms of congestive HF within 6 months of AMI in patients in whom myocardial perfusion was inadequate (MBG 0 and 1) after pPCI, Rasoul et al.[20] has reported a lack of correlation between the MBG and myocardial perfusion, as assessed by contrast echocardiography. The on-line available, operator independent software QuBE, reflects both the filling and emptying phase of the vessels by summing the maximum increase in gray value and the maximum decrease after that.[10] A QuBE score below the median value in DM patients in the present study was the only myocardial perfusion indicator, beyond MBG and STR which was associated with new-onset HF, increased all-cause mortality, and a combination of both adverse events. On multivariate proportional hazard modeling, however, QuBE was no longer an independent predictor of long-term adverse outcomes.

Of note, our patients with diminished myocardial perfusion (lower QuBE scores) or slower epicardial flow (higher corrected TIMI frame count) at the end of the interventional procedure had larger enzymatic infarct size and a significantly lower left ventricular EF afterwards. DM may contribute to this cycle through several pathophysiological mechanisms such as microangiopathy, dysfunctional endothelium,[21] increased expression of P-selectin[22] or intercellular adhesion molecule-1,[23] which augments the plugging of leukocytes in the capillaries, thereby creating an inflammatory, and pro-thrombotic milieu. Regardless of the manner in which the injury progresses, either linear or cascade, DM patients have a higher incidence of myocardial edema 48 hours post-myocardial infarction in T2 quantified magnetic resonance imaging[24] and a higher incidence of microvascular obstruction and a larger infarct size day 7 post-myocardial infarction based on late gadolinium enhanced magnetic resonance imaging.[25]

This study has several limitations. First, our sample size was small, and all subjects were recruited from 1 center, which may hamper the generalization of our findings. Even though the follow-up is long-term, the information was not derived from medical records but only from those reported by the NHF and death registry, which is why no echocardiography was performed to assess the type and severity of HF. Similarly, we did not have specific data on the cause of death which could have allowed us to hypothesize mechanisms for assessing the excess risk observed. There was also no information regarding new cases of DM collected during the 6-year follow-up. Our study patients were recruited before the introduction of new hypoglycemic drugs, such as sodium-glucose co-transporter 2 inhibitors,

and glucagon-like peptide-1 receptor agonists, which can improve cardiovascular outcomes, especially in patients with atherosclerotic cardiovascular disease and HF.[26] Further large-scale, prospective studies using current diabetes treatment drugs would be interest. Another point to consider is that in the course of recruitment and follow-up, pPCI technology has evolved, for example, the increasing use of radial access, improved drug-eluting stents, reduced use of adjunctive thrombectomy, and the introduction of new antiplatelet drugs.[27] All of our patients received clopidogrel as an adjunct to aspirin in the dual anti-platelet treatment, though ticagrelor now seems to be more effective in diabetic patients.[28,29]

In this 6-year follow-up study, type 2 DM and diminished myocardial perfusion increase the risk of HF and/or all-cause mortality during a 6-year follow-up following pPCI for STEMI.

Authors' Contribution

AT, KN, JG and ENK designed the research. AT, KN, JG and GL wrote paper. TM, ER, KP, TS, KN, HK, and AT were involved in the data collection and TM, ER, KP, TS, KN, HK, AT and GL in data analysis. All authors edited and approved the final version of the manuscript.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.10.051.

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