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Impact of elevated HbA1c on long-term mortality in patients presenting with acute myocardial infarction in daily clinical practice: insights from a 'real world' prospective registry of the Zwolle Myocardial Infarction Study Group

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Abstract

Background: Long-term clinical outcome is less well known in up to presentation persons unknown with diabetes mellitus who present with acute myocardial infarction and elevated glycosylated haemoglobin (HbA1c) levels on admission. We aimed to study the prognostic impact of deranged HbA1c at presentation on long-term mortality in patients not known with diabetes, presenting with acute myocardial infarction.

Methods: A single-centre, large, prospective observational study in patients with and without known diabetes admitted to our hospital for ST-segment elevation myocardial infarction (STEMI) and non-STEMI. Newly diagnosed diabetes mellitus was defined as HbA1c of 48 mmol/l or greater and pre-diabetes mellitus was defined as HbA1c between 39 and 47 mmol/l. The primary endpoint was all-cause mortality at short (30 days) and long-term (median 52 months) follow-up.

Results: Out of 7900 acute myocardial infarction patients studied, 1314 patients (17%) were known diabetes patients. Of the 6586 patients without known diabetes, 3977 (60%) had no diabetes, 2259 (34%) had pre-diabetes and 350 (5%) had newly diagnosed diabetes based on HbA1c on admission. Both short-term (3.9% vs. 7.4% vs. 6.0%, $p<0.001$) and long-term mortality (19% vs. 26% vs. 35%, $p<0.001$) for both pre-diabetes patients as well as newly diagnosed diabetes patients was poor and comparable to known diabetes patients. After multivariate analysis, newly diagnosed diabetes was independently associated with long-term mortality (hazard ratio 1.72, 95% confidence interval 1.27–2.34, $P=0.001$).

Conclusions: In the largest study to date, newly diagnosed or pre-diabetes was present in 33% of acute myocardial infarction patients and was associated with poor long-term clinical outcome. Newly diagnosed diabetes (HbA1c $\geqslant$48 mmol/mol) is an independent predictor of long-term mortality. More attention to early detection of diabetic status and initiation of blood glucose-lowering treatment is necessary.

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Introduction

Prognosis after acute myocardial infarction (AMI) in patients with diabetes mellitus (DM) is worse compared to patients without DM, even in the setting of optimal reperfusion strategy involving primary percutaneous coronary intervention (PCI).[1] Glycosylated haemoglobin (HbA1c) is an established marker of long-term glycaemic control in patients with DM, and elevated HbA1c levels in such patients are associated with an increased risk of future microvascular and macrovascular disease.[2,3] Moreover, Selvin et al. found that elevated HbA1c levels are also predictive of cardiovascular disease and mortality in patients without DM, irrespective of fasting glucose levels,[4] indicating that long-term glycometabolic derangement even in the sub-diabetic range is also associated with cardiovascular disease risk.

Acute glycometabolic derangement in non-diabetic patients with myocardial infarction has already been proved to be an independent predictor of prognosis.[5–10] However, until now, previous studies on the predictive value of HbA1c levels on mortality in non-diabetic and undiagnosed patients with AMI are limited due to small numbers, short follow-up, no correction for confounders, or the diagnosis being based on glucose level and not on HbA1c level, which is allowed now according to the current American Diabetes Association (ADA) guidelines.[11–16]

The aim of the present study was to assess the prevalence and prognostic impact of HbA1c levels in a large population of patients with new DM (based on HbA1c) or pre-DM (based on HbA1c) on long-term all-cause mortality in patients who were admitted to our hospital for ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). Furthermore, we want to create awareness among cardiologists to look critically at HbA1c in STEMI and NSTEMI patients when presenting and if necessary to diagnose and treat DM.

Research design and methods

Study design and population

We performed a retrospective analysis of data from a prospective observational study in an all-comer STEMI and NSTEMI population.

All consecutive patients admitted with STEMI and NSTEMI in Isala (Zwolle, The Netherlands) between January 2006 and January 2015 were included. During this timeframe, HbA1c was routinely measured directly on admission in all STEMI and NSTEMI patients. In order to maintain a uniform patient population with STEMI and NSTEMI, specific inclusion and exclusion criteria were applied. NSTEMI was defined as acute chest pain or a dyspnoae equivalent, in combination with a rise or fall in cardiac troponin/creatine kinase (CK)/CK-MB compatible with myocardial infarction (MI), and/or dynamic ST or T-wave changes.

Furthermore, NSTEMI patients were only included if the NSTEMI was causes by acute atherothrombotic coronary artery disease and usually precipitated by atherosclerotic plaque disruption (rupture or erosion). Furthermore, only patients who presented after an out-of-hospital cardiac arrest or in-hospital cardiac arrest were excluded, as prognosis in these patients is primarily driven by neurological outcome. There were no further exclusion criteria with regard to age, gender, ischaemic time, cardiac history or renal function.

Data collection

Patient characteristics were acquired on admission using either case record forms or using a computer-based database. Clinical follow-up was performed by telephone contact (with either the general practitioner or with direct contact with patients) or through coupling of municipal mortality records. Follow-up was performed by independent research nurses not involved in patient treatment, as has been standard practice in our department for many years.[17–19] Ten patients (10/7900=0.001%) were lost to follow-up for long-term all-cause mortality. A total of 568 patients (568/7900=7.2%) were lost to follow-up for one year major adverse cardiac events (MACEs). Informed consent was obtained from each patient. Study approval was obtained from the medical ethics committee of our hospital.

Measurements

DM definition by HbA1c was determined by using current ADA guidelines.[16] Patients without diabetes (no DM) were defined as a HbA1c level at admission of less than 39 mmol/mol (<5.7%). Patients with pre-DM were defined by a HbA1c level on admission of 39–47 mmol/mol (5.7–6.4%). Newly diagnosed DM patients were defined by a HbA1c level of 48 mmol/mol or greater (≥6.5%). Known DM patients were defined as known with diabetes on admission, treated either with a diet, with oral glucose-lowering medication and/or with insulin, irrespective of HbA1c.

Ischaemic time was defined as the time between symptom onset and first balloon inflation. The thrombolysis in

myocardial infarction (TIMI) scoring system was used to refer to coronary blood flow assessed during PCI.[20] Myocardial blush grade (MBG), an angiographic measure of myocardial perfusion, was defined as previously described.[21] Successful PCI was defined as TIMI 3 flow with MBG 2–3 after PCI. Myocardial infarct size was measured by peak CK level in the first 24 hours after admission. Definition of re-infarction was in accordance with the most recent universal definition of MI.[22] MACEs were defined as cardiac mortality, re-infarction and target lesion revascularisation.

HbA1c levels were measured on the Primus Ultra 2 affinity chromatography high-pressure liquid chromatography (HPLC) (Primus Diagnostics, Kansas City, MO, USA) in Zwolle with a within-run coefficient of variation (CV) of less than 0.5% and Premier Hb9210, affinity chromatography HPLC, IFCC and NGSP certified (Trinity Biotech); and Tosoh G8, cation-exchange HPLC, IFCC certified (Tosoh Bioscience).[3]

Glucose levels were measured on a modular device (Roche Diagnostics) with venous blood, and with a Radiometer ABL 700/800 series analyser (Radiometer Copenhagen) in whole-blood arterial samples.[23] The glomerular filtration rate (GFR) was estimated using the modification of diet in renal disease equation.

Primary outcome

The clinical primary endpoint for our current study was long-term all-cause mortality.

Secondary outcome

The secondary endpoint for our current study was one-year MACEs.

Statistical analysis

Patient groups were created according to DM status and admission HbA1c lower than 39 mmol/mol, 39–47 mmol/mol and higher than 47 mmol/mol. Continuous data were summarised and are described using median values with the corresponding interquartile range (IQR), or as mean values with corresponding standard deviation (SD), and dichotomous data are given as counts and percentages. Mortality data were compared using either chi-square or log-rank analysis for comparison of Kaplan–Meier actuarial survival curves, where appropriate. Differences between continuous data were non-parametric tested by use of the Kruskal–Wallis test, and the chi-square test was used as appropriate for dichotomous data.

In multivariate analysis (Cox regression) the association between HbA1c and the primary outcome (long-term all-cause mortality) was adjusted for other (baseline) characteristics, including age, sex, prior coronary artery bypass grafting (CABG) or prior MI, smoking, hypertension, renal function, recruitment period (per year), STEMI at admission, Killip class, PCI performed, CABG performed and multivessel disease. Kaplan–Meier curves were constructed for overall all-cause mortality. All the statistical analyses were performed using SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA) for Windows, version 24.0. A P value less than 0.05 was considered statistically significant.

Results

Patient characteristics

A detailed description of baseline and angiographic characteristics are presented in Table 1.

A total number of 7900 patients were included in the present analysis, of which 1314 (17%) had known DM at presentation. Of the 6586 patients without known DM, 3977 (60%) had no DM, 2259 (34%) had pre-DM and 350 (5%) had newly diagnosed DM based on HbA1c concentrations on admission, Figure 1. Mean HbA1c concentration among patients with pre-DM was 41.7 (±2.2) mmol/mol, 60.6 (±16.0) mmol/mol among patients with newly diagnosed DM and 54.9 (±13.6) mmol/mol among patients with known DM. The glucose level on admission was highest among patients with newly diagnosed DM (12.4±4.8 mmol/l, $P<0.001$). Furthermore, inflammation levels measured by C-reactive protein on admission were significantly higher in patients with pre-DM, newly diagnosed DM and known DM when compared to no DM patients (14.6 vs. 19.1 vs. 19.9 vs. 11.4 mg/L, $P<0.001$). Moreover, body mass index levels were significantly higher in patients with pre-DM, newly diagnosed DM and known DM as compared to patients without DM (27.1 vs. 28.8 vs. 28.7 vs. 26.5 kg/m², $P<0.001$).

When compared to patients without DM, patients with pre-DM and newly diagnosed DM more often presented with NSTEMI (32.2% vs. 39.3% vs. 44.9%, $P<0.001$) and significantly more often had hypertension, hypercholesterolemia and a previous history of MI, PCI or CABG, see Table 1. Interestingly, pre-DM patients and newly diagnosed DM patients, as well as known DM patients, more often presented with signs of acute heart failure (Killips class 2 or more) on admission ($P<0.001$).

Ischaemic time and multivessel disease were significantly higher in pre-DM and newly diagnosed DM patients compared to patients without DM (both $P<0.001$). There were no differences in TIMI 3 flow post-PCI ($P=0.729$), successful PCI ($P=0.057$) or the use of intra-aortic balloon pump ($P=0.649$) between patients with pre-DM or newly diagnosed DM and patients without DM.

Table 1. Baseline and angiographic characteristics.

	No DM	Pre DM	Newly diagnosed DM	Known DM	*P* value
	N=3977	*N*=2259	*N*=350	*N*=1314	
Patient demographics					
Age (years), mean±SD	62.9 ± 13.1	68.2 ± 12.5	67.3 ± 12.9	70.1 ± 11.2	<0.001
Male sex	2955/3977 (74.3)	1500/2259 (66.4)	245/350 (70.0)	819/1314 (62.3)	<0.001
Body mass index (kg/m^2)	26.5 ± 3.8	27.1 ± 4.2	28.8 ± 4.7	28.7 ± 4.9	<0.001
Medical history					
Prior MI	338/3968 (8.5)	329/2254 (14.6)	59/350 (16.9)	275/1307 (21.0)	<0.001
Prior PCI	322/3974 (8.1)	327/2256 (14.5)	55/350 (15.7)	274/1311 (20.9)	<0.001
Prior CABG	171/3976 (4.3)	156/2259 (6.9)	37/350 (10.6)	183/1312 (13.9	<0.001
Risk factors					
Active smoker	1480/3961 (37.4)	799/2244 (35.6)	110/350 (31.5)	335/1298 (25.8)	<0.001
Positive family history	1563/3964 (39.4)	694/2254 (30.8)	118/350 (33.7)	375/1306 (28.7)	<0.001
Hypertension	1460/3968 (36.8)	1031/2256 (45.7)	172/350 (49.1)	885/1311 (67.5)	<0.001
Hypercholesterolemia	765/3946 (19.4)	580/2243 (25.9)	83/349 (23.8)	649/1297 (50.0)	<0.001
Haemodynamics					
Blood pressure, systolic (mmHg)	135.3 ± 25.2	136.4 ± 26.9	137.6 ± 26.4	138.0 ± 26.7	0.004
Blood pressure, diastolic (mmHg)	81.7 ± 20.5	80.6 ± 18.6	82.3 ± 16.1	79.7 ± 27.0	<0.001
Pulse (beats/min)	75.0 ± 18.4	77.3 ± 20.1	84.4 ± 24.4	82.5 ± 31.4	<0.001
Acute myocardial infarction					
STEMI	2692/3977 (67.7)	1371/2259 (60.7)	193/350 (55.1)	599/1314 (45.6)	<0.001
NSTEMI	1285/3977 (32.2)	888/2259 (39.3)	157/350 (44.9)	715/1314 (54.4)	<0.001
Killip class					
Killip 1	3175/3423 (92.8)	1501/1730 (86.8)	216/272 (79.4)	841/1090 (77.2)	<0.001
Killip 2	132/3423 (3.9)	96/1730 (5.5)	25/272 (9.2)	103/1090 (9.4)	<0.001
Killip 3	96/3423 (2.8)	109/1730 (6.3)	21/272 (7.7)	121/1090 (11.1)	<0.001
Killip 4	20/3423 (0.6)	24/1730 (1.4)	9/249 (3.6)	25/1090 (2.3)	<0.001
Biochemical tests results					
HbA1c (mmol/mol)	35.7 ± 2.3	41.7 ± 2.2	60.6 ± 16.0	54.9 ± 13.6	<0.001
Glucose (mmol/L)	7.7 ± 2.1	8.2 ± 2.3	12.4 ± 4.8	11.9 ± 4.9	<0.001
C-reactive protein (mg/L)	11.4 ± 29.9	14.6 ± 37.0	19.1 ± 43.5	19.9 ± 41.9	<0.001
eGFR (ml/min/1.73m^2)	96.8 ± 37.1	87.1 ± 39.4	97.4 ± 48.0	84.2 ± 42.2	<0.001
Angiographic characteristics					
Total ischaemic time >6 hours	1369/3538 (38.7)	834/1949 (42.8)	144/288 (50.0)	572/1015 (56.4)	<0.001
Underwent coronary angiography	3705/3874 (95.6)	2062/2206 (93.5)	313/344 (91.0)	1112/1273 (87.4)	<0.001
Multi-vessel coronary disease	1705/3424 (49.8)	1083/1955 (55.4)	175/299 (58.5)	732/1039 (70.5)	<0.001
Infarct-related vessel					
RCA	1201/3310 (36.3)	677/1836 (36.9)	94/284 (33.1)	324/924 (35.1)	0.560
LAD	1353/3310 (40.9)	701/1836 (38.2)	105/284 (37.0)	337/924 (36.5)	0.043
CX	637/3310 (19.2)	364/1836 (19.8)	61/284 (21.5)	170/924 (18.4)	0.650
Other	119/3310 (3.6)	94/1836 (5.1)	24/284 (8.5)	93/924 (10.1)	<0.001
TIMI 3 pre-PCI	947/2888 (32.8)	554/1598 (34.7)	86/242 (35.5)	323/751 (43.0)	<0.001
Underwent PCI	2934/3737 (78.5)	1637/2110 (77.6)	247/320 (77.2)	770/1159 (66.4)	<0.001
TIMI 3 post-PCI	2717/2884 (94.2)	1500/1594 (94.1)	222/239 (92.9)	713/752 (94.8)	0.729
Successful PCI	2767/2886 (95.9)	1511/1601 (94.4)	227/240 (94.6)	709/754 (94.0)	0.057
Stent placed	2475/3660 (67.6)	1349/2079 (64.9)	213/314 (67.8)	617/1131 (54.6)	<0.001
IABP in situ	210/3742 (5.6)	102/2094 (4.9)	18/329 (5.5)	67/1182 (5.7)	0.649
Underwent CABG	415/3874 (10.7)	286/2206 (13.0)	37/344 (10.8)	199/1274 (15.6)	<0.001
Medical therapy	540/3874 (13.9)	288/2206 (13.1)	51/344 (14.8)	242/1273 (19.0)	<0.001
Infarct size					
Peak CK in the first 24 hours	1047.0 ± 1551.8	977.0 ± 1470.7	1025.6 ± 1464.1	791.8 ± 1286.2	<0.001

Table 1. (Continued)

	No DM	Pre DM	Newly diagnosed DM	Known DM	*P* value
	N=3977	*N*=2259	*N*=350	*N*=1314	
Discharge medication					
Dual antiplatelet treatment	2757/3621 (76.1)	1521/2103 (72.3)	227/317 (71.6)	752/1195 (62.9)	<0.001
Beta-blockers	3178/3621 (87.8)	1852/2103 (88.1)	283/317 (89.3)	1027/1195 (85.9)	0.225
ACE inhibitors	2099/3621 (58.0)	1237/2103 (58.8)	198/317 (62.5)	643/1195 (53.8)	0.009
Statin	3134/3621 (86.6)	1793/2103 (85.3)	273/317 (86.1)	967/1195 (80.9)	<0.001
Diuretics	565/3621 (15.6)	489/2103 (23.3)	95/317 (30.0)	461/1195 (38.6)	<0.001
Oral glucose-lowering medication	6/3621 (0.2)	21/2103 (1.0)	89/317 (28.1)	716/1195 (59.9)	<0.001
Insulin	9/3621 (0.2)	11/2103 (0.5)	44/317 (13.9)	453/1195 (37.9)	<0.001
Any medication for DM	15/3621 (0.4)	32/2103 (1.5)	110/317 (34.7)	969/1195 (81.1)	<0.001

Data are *n*/*N* (%) or mean (standard deviation; SD), or median (interquartile range; IQR).
DM: diabetes mellitus; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; LAD: left anterior descending artery; RCX: ramus circumflex artery; RCA: right coronary artery; HbA1c: glycosylated haemoglobin; eGFR: estimated glomerular filtration rate; TIMI: thrombolysis in myocardial infarction; IABP: intra-aortic balloon pump.

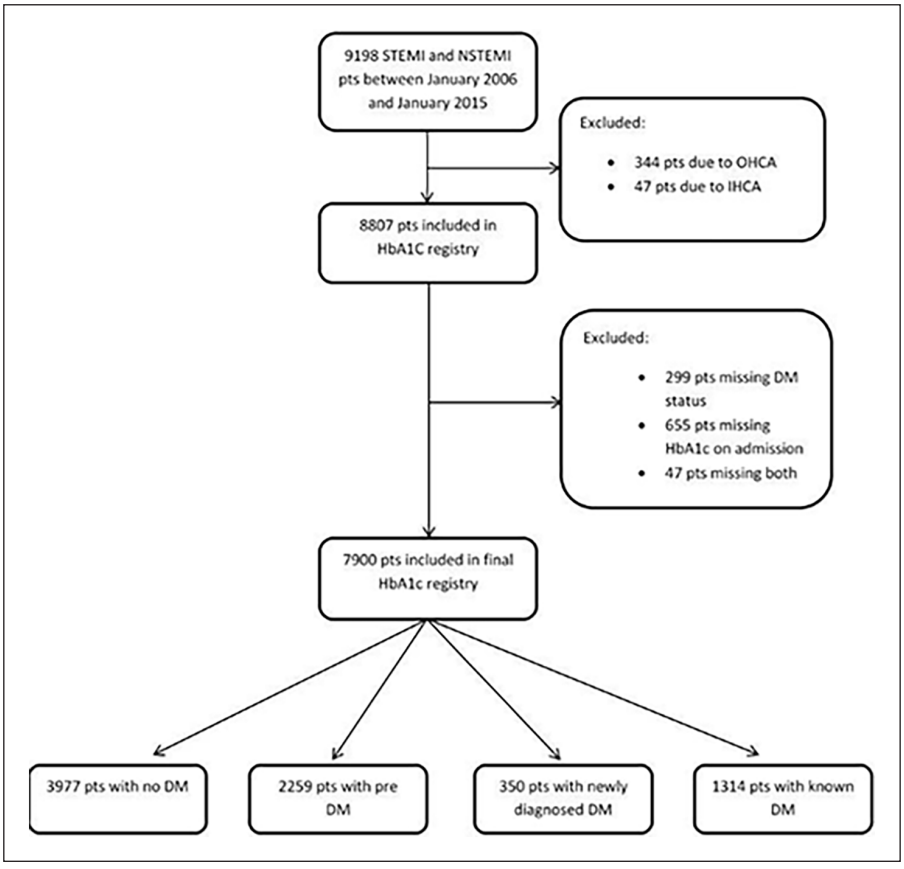

Figure 1. Flowchart.

With regard to medication at discharge, dual antiplatelet therapy (DAPT) was described less often in pre-DM patients and patients with newly diagnosed DM when compared to no DM patients (72.3% vs. 71.6% vs. 76.1%, $P<0.001$).

Furthermore, of patients with newly diagnosed DM, 28.1% had oral glucose-lowering medication at discharge, 13.9% of them had insulin at discharge and 34.7% had oral glucose-lowering medications and insulin for the treatment of DM.

Table 2. Clinical outcomes.

	No DM	Pre-DM	Newly diagnosed DM	Known DM	*P* value
	N=3972	*N*=2257	*N*=350	*N*=1311	
Follow-up length (months)	59.1 ± 30.3	45.4 ± 28.9	44.4 ± 29.8	44.8 ± 31.5	<0.001
All-cause mortality					
30-day mortality	113/3970 (2.8)	87/2256 (3.9)	26/350 (7.4)	79/1311 (6.0)	<0.001
One-year mortality	210/3972 (5.3)	184/2257 (8.2)	44/350 (12.6)	196/1311 (15.0)	<0.001
Long-term mortality (primary endpoint)	594/3972 (15.0)	423/2256 (18.7)	92/350 (26.3)	455/1311 (34.7)	<0.001
Re-infarction					
30-day re-infarction	20/3712 (0.5)	13/2000 (0.7)	0/299 (0.0)	26/1217 (2.1)	<0.001
One-year re-infarction	50/3712 (1.3)	32/2002 (1.6)	2/299 (0.7)	41/1217 (3.4)	<0.001
TLR					
30-day TLR	455/3730 (12.2)	328/2034 (16.1)	36/303 (11.9)	211/1226 (17.2)	0.001
One-year TLR	556/3730 (14.9)	378/2036 (18.6)	47/303 (15.5)	250/1226 (20.4)	0.001
MACEs					
30-day MACE	562/3732 (15.1)	412/2038 (20.2)	61/306 (19.9)	294/1228 (23.9)	<0.001
One-year MACE	749/3740 (20.0)	553/2046 (27.0)	90/312 (28.8)	430/1234 (34.8)	<0.001

DM: diabetes mellitus; TLR: target lesion revascularisation; MACEs: major adverse cardiac events (all=cause mortality/re-infarction/TLR).

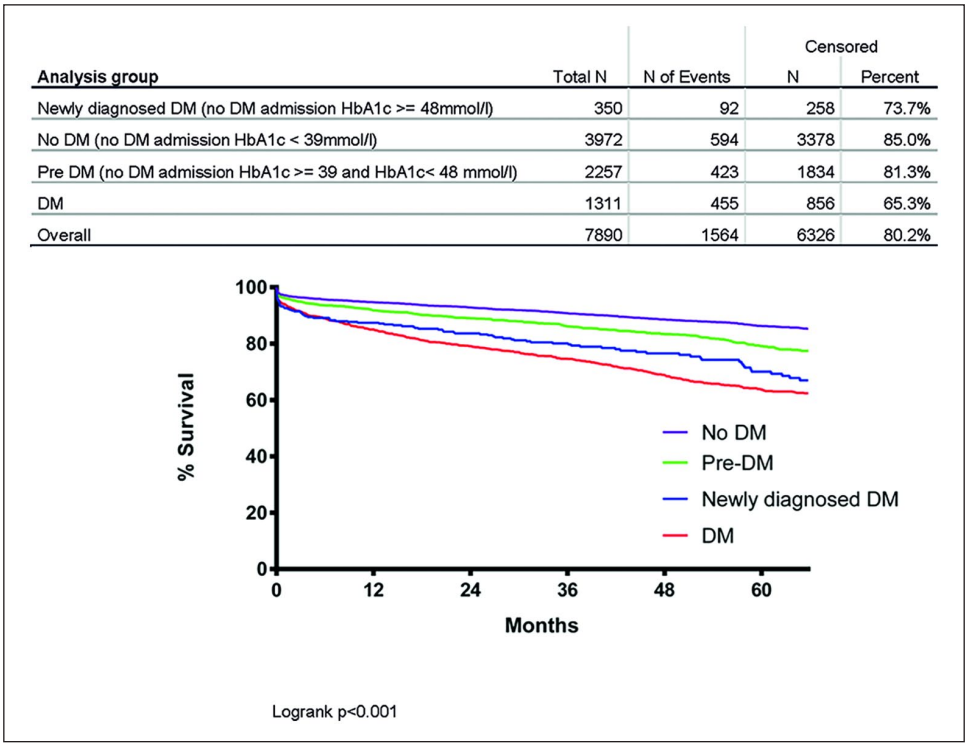

Figure 2. Kaplan–Meier survival curve.

Clinical outcome

The clinical outcomes are presented in Table 2 and Figures 2 and 3. Patients without DM significantly more often underwent coronary angiography ($P<0.001$) and subsequent PCI ($P<0.001$) and less frequent CABG ($P<0.001$) or medical therapy ($P<0.001$) as treatment when compared to the other three groups.

In the patients who underwent PCI there were no differences in the initial PCI result, although the 30-day and one1-year re-infarction rates were significantly higher in

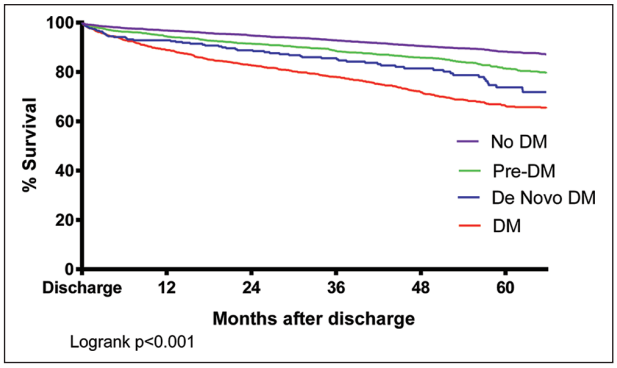

Figure 3. Landmark analysis: cumulative risk of all-cause mortality of patients who were alive at discharge for all four patient groups.

pre- DM, newly diagnosed DM and known DM patients when compared to patients without DM ($P<0.001$). One-year target lesion revascularisation rates were significantly higher in pre-DM, newly diagnosed DM and known DM patients when compared to patients without DM ($P<0.001$).

Furthermore, 30-day and one-year MACEs ($P<0.001$ for both) were significantly higher in pre-DM, newly diagnosed DM and known DM patients when compared to no DM patients. The 30-day and one-year mortality among patients with newly diagnosed DM were 7.4% and 12.6%, respectively. Comparably, 30-day and one-year all-cause mortality rates among patients with known DM were 6.0% and 15.0%, were 3.9% and 8.2% in patients with pre-DM, and were lowest at 2.8% and 5.3% among patients without DM ($P<0.001$ for both).

The primary endpoint, long-term all-cause mortality (median 52 months; IQR 26–79 months) was significantly higher in the newly diagnosed DM group (26.3%) and pre-DM group (18.7%) as compared to the no DM group (15%), and was highest in the group with known DM (34.7%) ($P<0.001$), as is also illustrated by a Kaplan–Meier curve, see Figure 2. Furthermore, as shown in Figure 3, a landmark analysis for the primary endpoint was performed for the patients who were discharged alive, which underlined the same finding.

Using multivariate Cox regression analysis to correct for baseline characteristics, haemodynamic parameters and angiographic characteristics, newly diagnosed DM (HbA1c level ⩾48 mmol/l on admission) was independently associated with long-term mortality (hazard ratio 1.72, 95% confidence interval 1.27–2.34, $P=0.001$). Significant predictors are presented in Table 3.

Table 3. Multivariate Cox-regression analysis for long-term all-cause mortality.

	STEMI/NSTEMI patients with Hba1C measurement ($N=5066$)		
	HR	95% CI	*P* value
Age (per decade)	2.15	1.97-2.33	<0.001
Male gender	1.17	1.01-1.36	0.034
eGFR <60	1.58	1.34-1.85	<0.001
Smoking	1.41	1.20-1.65	<0.001
Hypertension	1.15	1.00-1.32	0.043
Previous CABG	1.41	1.13-1.76	0.002
Previous MI	1.20	1.00-1.45	0.048
Analysis group	0.00	0.00-0.00	<0.001
Newly diagnosed DM vs. no DM	1.72	1.27-2.34	0.001
Pre-DM vs. no DM	1.04	0.88-1.23	0.669
Known DM vs. no DM	1.70	1.43-2.02	<0.001
Killip class			<0.001
Killip 2 vs. Killip 1	1.93	1.54-2.41	<0.001
Killip 3 vs. Killip 1	2.48	1.94-3.17	<0.001
Killip 4 vs. Killip 1	5.55	3.78-8.14	<0.001
Recruitment period (per year)	0.94	0.91-0.98	0.004
CABG	0.77	0.61-0.97	0.027
PCI	0.95	0.78-1.16	0.622
Multivessel disease	1.28	1.10-1.49	0.002
STEMI vs. NSTEMI	1.27	1.09-1.48	0.002

DM: diabetes mellitus; HR: hazard ratio; CI: confidence interval; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; HbA1c: glycosylated haemoglobin; eGFR: estimated glomerular filtration rate; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction.

Discussion

Main important findings

Our study, the largest study to date, demonstrates that 33% of AMI patients have a disorder in long-term glycaemic control as measured by HbA1c (4% newly diagnosed diabetes, 29% pre-diabetes). Moreover, newly diagnosed diabetes is associated with a significantly worse short and long-term prognosis, which interestingly is as poor as in patients with known DM. Of significance, this study highlights that newly diagnosed diabetes is an independent predictor of long-term mortality.

Recent studies which have evaluated the prognostic value of HbA1c in patients previously unknown with DM hospitalised with ACS have reported discrepant results. In three studies HbA1c did not prove to be an independent predictor of mortality.[12,24,25] On the other hand, two other studies found that HbA1c was an independent predictor of mortality.[14,26] A systematic review found that HbA1c levels had different prognostic effects based on patients' diabetes status, whereas a U-shaped relationship, with lower mortality among patients within the pre-DM range has been observed.[27]

With regard to predicting cardiovascular risk in adults without diabetes, Selvin et al.[4] demonstrated improved risk reclassification for coronary heart disease with the inclusion of HbA1c in fully adjusted models, suggesting that HbA1c may be superior to fasting glucose for characterising long-term risk.

Our study represents a large dataset, utilising several years of routine admission HbA1c measurements in all STEMI and NSTEMI patients, and so provides a unique insight into the natural history of glycaemic derangement on long-term mortality in a large group of ACS patients. Our study shows that without routine HbA1c measurement on admission, a significant proportion (33%) of ACS patients with impaired glucose metabolism would go unnoticed, thus missing an opportunity properly to address such derangements through lifestyle adjustments and/or medication. Our findings suggest the need for the adjustment of standard protocols in our hospital and probably many others too.

High-risk patients

Newly diagnosed DM and pre-DM patients, as represented by our data, are truly a high ischaemic risk patient population, as manifested by a higher cardiovascular risk profile. They more frequently have a history of previous MI, previous PCI and previous CABG. Furthermore, on coronary angiography, when compared to patients without DM, they significantly more often have multivessel coronary disease.

Furthermore, in the subset of STEMI patients in our database, patients with newly diagnosed diabetes have a higher prevalance of previous cardiac events, and they present later in the hospital (resulting in a longer total ischaemic time). In a considerable subset of patients with diabetes, clinical signs of MI may present differently with less or even absent pain sensations. This different presentation is ascribed to the presence of neuropathy. Although this might be a possible explanation in newly diagnosed DM as well, this seems less probable, because the development of neuropathy takes years of glycometabolic dysregulation. Such a long-term undetected dysregulation would be quite rare in our opinion.

Treatment and recommendation

With this routine HbA1c measurement on admission in this large AMI cohort we identified 350 patients with newly diagnosed DM. However, only 34.7% of them received any DM medication (oral and/or insulin) at discharge. Adequate treatment in recently diagnosed patients with diabetes is of paramount importance. Svensson et al. recently showed that adequate treatment attaining a strict HbA1c goal of less than 48 mmol/l within 6 months in recently diagnosed DM patients treated with metformin (currently the first oral blood glucose-lowering agent of choice according to the ADA guidelines) was associated with a significantly lower risk of cardiovascular events and mortality, with cardiovascular risk gradually increasing at higher HbA1c levels.[28]

So, this population (newly diagnosed DM and pre-DM patients) may need better follow-up and treatment in the post-infarct trajectory of glucose dysregulation which is in accordance with the European Society of Cardiology (ESC) guidelines.[29]

Other risk factors such as hypertension and overweight would also need more attention when taking into account the more frequent occurrence of overweight and hypertension in the pre-DM and newly diagnosed DM population. Early identification of high HbA1c concentrations enables the initiation of specific intervention strategies and may help us develop strategies to improve prognosis in these high-risk patient groups. This is of particular importance because there is a global increase in the number of patients with cardiovascular disease with pre-diabetes, newly diagnosed diabetes, underlying insulin resistance and overt diabetes mellitus. Both glucose and HbA1c should be measured routinely in patients admitted with ACS.

Limitations

This study was from a single-centre registry and has the intrinsic limitations of a registry.

A patient already diagnosed with and properly treated for DM could have a lower risk than a patient whose DM status is diagnosed only at the time of hospital admission for NSTEMI or STEMI. We have not been able to make a subdivision into type 1 and type 2 DM in known diabetes patients.[30]

Although the current ADA guidelines accept HbA1c as diagnostic criteria, it should be mentioned that the use of HbA1c for the diagnosis of DM is a subject of discussion.[31] Furthermore, almost 20% of known DM patients did not receive any blood glucose medication at discharge and 65% of the newly diagnosed DM patients did not have blood glucose medication at discharge.

Conclusions

In the largest study to date, newly diagnosed diabetes or pre-diabetes was present in 33% of AMI patients and both, but mainly newly diagnosed diabetes was associated with poor long-term clinical outcome compared to patients with known diabetes. Newly diagnosed diabetes (HbA1c $\geqslant$48 mmol/mol) is an independent predictor of long-term mortality. More attention to the early detection of present diabetes and the possible start of blood glucose-lowering treatment is necessary.

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Conflict of interest

The authors declare that there is no conflict of interest.

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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