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ORIGINAL RESEARCH

Admission Glucose Levels and Associated Risk for Heart Failure After Myocardial Infarction in Patients Without Diabetes

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BACKGROUND: Dysglycemia at acute myocardial infarction (AMI) is common and is associated with mortality. Information on other outcomes is less well explored in patients without diabetes in a long-term perspective. We aimed to explore the relationship between admission glucose level and long-term outcomes in patients with AMI without diabetes in a nationwide setting.

METHODS AND RESULTS: Patients without diabetes (n=45 468) with AMI registered in SWEDEHEART (Swedish Web–System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) and admission glucose ≤11 mmol/L (≤198 mg/dL) were followed for outcomes (AMI, heart failure, stroke, renal failure, and death) between 2012 and 2017 (mean follow-up time 3.3±1.7 years). The association between categorized glucose levels and outcomes was assessed in adjusted Cox proportional hazards regression analyses (glucose levels 4.0–6.0 mmol/L [72–109 mg/dL] as reference). Further nonfatal complications and their associated mortality were explored (patients without events served as a reference). A glucose level of 7.8–11.0 mmol/L (140–198 mg/dL) was associated with hospitalization for heart failure (hazard ratio [HR] 1.40 [95% CI, 1.30–1.51], *P*<0.001), renal failure (1.17; 1.04–1.33, *P*=0.009), and death (1.31; 1.20–1.43, *P*<0.001), but not with recurrent myocardial infarction (0.99; 0.92–1.07, *P*=0.849) or stroke (1.03; 0.88–1.19, *P*=0.742). Renal failure had the strongest association with future mortality (age-adjusted HR 4.93 [95% CI, 4.34–5.60], *P*<0.001), followed by heart failure (3.71; 3.41–4.04, *P*<0.001), stroke (3.39; 2.94–3.91, *P*<0.001), and myocardial infarction (2.08; 1.88–2.30, *P*<0.001).

CONCLUSIONS: Elevated glucose levels at AMI admission identifies patients without diabetes at increased risk of long-term complications: in particular, hospitalization for heart and renal failure. These results emphasize that glucose levels at admission could be useful in risk assessment after myocardial infarction.

Key Words: admission glucose ■ heart failure ■ myocardial infarction ■ prognosis

It is well known that elevated glucose levels at admission are associated with increased mortality when patients are hospitalized for acute myocardial infarction (AMI) as well as for other diagnoses such as infectious diseases in both patients with and without diabetes.[1–7] Information on outcomes other than mortality in a contemporary setting is less well explored in a long-term perspective, especially in patients without diabetes. Observational cohort studies have identified undiagnosed prediabetes and diabetes as being common in patients with cardiovascular disease when investigated at discharge, especially in those with myocardial infarction (MI) and heart failure (HF).[8–10] In patients with AMI, there are divergent findings on whether newly detected dysglycemia is associated with adverse outcome, where some report an increased risk[5,11–13] and others have found no associated increased risk.[14,15] In patients with HF, there are more robust associations between prediabetes and a poorer prognosis.[16]

During the 1980s to 1990s, admission glucose at AMI was regarded as an important prognostic marker,[5,17–19]

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CLINICAL PERSPECTIVE

What Is New?

- In this large, nationwide, observational study, admission glucose levels in patients without diabetes were associated with an increased risk in particular of cardiorenal (heart failure and renal failure) events after an acute myocardial infarction.
- This finding extends previous knowledge on admission glucose as a risk marker not only of short-term mortality but also of long-term major adverse events, starting already at mild hyperglycemia in patients without diabetes.

What Are the Clinical Implications?

- For now, admission glucose levels should be considered to be included in the risk assessment after myocardial infarction.
- Future clinical studies should investigate whether cardioprotective drugs known to reduce cardiorenal events also have prognostic beneficial effects in a similar acute myocardial infarction cohort without diabetes with hyperglycemia.

Nonstandard Abbreviations and Acronyms

MACE	major adverse cardiovascular events
NPR	National Patient Registry
OGTT	oral glucose tolerance test
SCAAR	Swedish Coronary Angiography and Angioplasty Registry

but emphasis on this marker has diminished with the development of cardiac-specific biomarkers, such as high-sensitivity troponin and N-terminal pro-B-type natriuretic peptide. Furthermore, the development of modern acute coronary care has resulted in a shorter hospital stay, reducing the opportunity to explore glucose disturbances before discharge and therefore possibly missing the opportunity to identify a high-risk group.[20]

We hypothesized that admission glucose levels in patients without diabetes could be a useful marker of impaired long-term prognosis after an AMI and explored the complication pattern in a large, contemporary, and nationwide setting.

METHODS

The authors declare that all supporting data are available within the article (and its online supplementary files).

Data Sources and Selected Patient Cohort

Patients with a physician-judged AMI (non–ST-segment–elevation myocardial infarction, or ST-segment–elevation myocardial infarction) admitted to a cardiac care unit, registered in SWEDEHEART (Swedish Web–System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) (RIKS-HIA) and undergoing a coronary angiography reported in the SCAAR (Swedish Coronary Angiography and Angioplasty Registry) in 2012 to 2017, with available glucose *reported on the first day* of AMI hospitalization, were included in the study (Figure 1). Patients who died during the first 30 days were excluded. Patients with glucose levels <2 mmol/L (36 mg/dL) and >30 mmol/L (540 mg/dL) were excluded from further analyses. Blood samples were drawn with patients in a fasting state for the majority of the patients, during the first 24 hours of admission. Blood glucose was analyzed at the hospital laboratory according to standardized methods. Analyses were based on data derived from the patient's first coronary angiography during the study period; readmissions were thus excluded. The patients were followed prospectively for hospitalization for AMI, stroke, HF, and renal failure until December 31, 2017 and all-cause death until June 30, 2018. Data on outcomes after the index AMI were collected from the SWEDEHEART registry and the NPR (National Patient Registry), while data on all-cause mortality were collected from the Swedish Population Register. No patient was lost to follow-up.

Definitions

Diabetes: Information on diabetes status was obtained from reported data in SWEDEHEART (SCAAR and RIKS-HIA) and from the NPR with *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes (E10-E14). Patients with a diabetes diagnosis before the index AMI were not included in the study.

Patients without diagnosed diabetes was defined as the absence of a diabetes diagnosis in SWEDEHEART (SCAAR and RIKS-HIA) and NPR. In addition, glucose levels of <2 mmol/L (36 mg/dL) and >30 mmol/L (540 mg/dL) were considered outliers and were therefore not included. Furthermore, patients with glucose levels of >11 mmol/L (198 mg/dL) were analyzed separately and were not included in the main analysis in order to create an pure group without diabetes. In patients without diabetes, glucose levels between 2 and 11 mmol/L (36–198 mg/dL) were categorized in the following 5 groups according to the definitions of hypoglycemia[21] and the World Health Organization

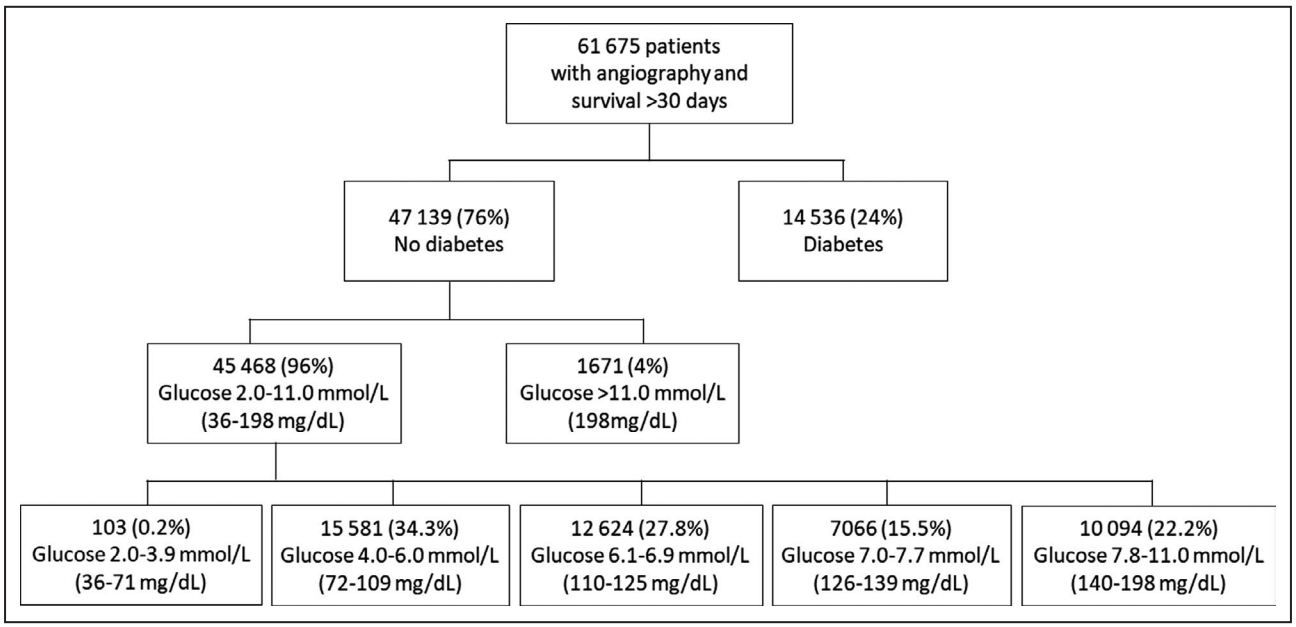

Figure 1. Flow chart of patient selection.

criteria for hyperglycemia and definition of prediabetes/diabetes[22]:

Group I glucose 2.0–3.9 mmol/L (36–71 mg/dL).
Group II glucose 4.0–6.0 mmol/L (72–109 mg/dL).
Group III glucose 6.1–6.9 mmol/L (110–125 mg/dL).
Group IV glucose 7.0–7.7 mmol/L (126–139 mg/dL).
Group V glucose 7.8–11.0 mmol/L (140–198 mg/dL).

Outcome

All-cause death until June 30, 2018 was collected from the Swedish Population Register.

Hospitalization for HF (defined as a hospitalization with a diagnosis of HF; *ICD-10* code I50), *stroke* (defined as ischemic stroke; *ICD-10* code I63), *myocardial infarction* (*ICD-10* code I21-I22), and *renal failure* (*ICD-10* code I12.0, N13.2, N17, N18, N19.9, N99.0) until December 31, 2017 was collected from the NPR. Renal failure includes acute renal failure, chronic renal failure, hypertensive renal failure, and unspecified renal disease but not renal failure requiring dialysis.

Major adverse cardiovascular events (MACE) includes first occurrence of MI, stroke, HF, and all-cause death.

We further categorized events as *atherothrombotic* (including MI or stroke) and *cardiorenal events* (defined as hospitalization with either HF or renal failure).

Statistical Analysis

Baseline characteristics were analyzed in patients without diagnosed diabetes stratified for glucose levels and presented as the median and interquartile range for continuous variables and numbers and percentages for categorical variables. To compare baseline characteristics between the different groups, χ^2 or Fisher exact test was used. Cumulative event rates for different clinical outcomes stratified by glucose levels were estimated using the Kaplan–Meier method. In addition, prognosis was analyzed stratified for glucose above and ≤11 mmol/L (198 mg/dL). The association between groups of glucose levels and future events was assessed in an adjusted Cox proportional hazards model, where Group II (glucose 4.0–6.0 mmol/L [72–109 mg/dL]) served as a reference. Hazard ratios (HR, 95% CI) were adjusted for age, sex, smoking, creatinine, previous diagnosis of MI/HF/CABG/cancer/dementia/dialysis/hypertension/chronic obstructive pulmonary disease/renal failure/stroke/peripheral artery disease, year, indication (non–ST-segment–elevation myocardial infarction/ST-segment–elevation myocardial infarction), hospital, angiographic findings, primary decision after angiography, cardiac shock, and medications at discharge (angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist, lipid-lowering agents, aspirin, β-blockade, oral anticoagulant, and other antiplatelet therapy). We also assessed the association between continuous glucose levels and outcomes using a restricted cubic spline with 4 knots across the spectrum of glucose levels between 2 and 21 mmol/L (36–378 mg/dL). A glucose level of 5.0 mmol/L (90 mg/dL) served as a reference with HR 1.0. Similar analyses for hemoglobin A1c

(HbA1c) were performed in a subgroup of patients, where HbA1c 38 mmol/mol (Diabetes Control and Complications Trial 5.6%) served as the reference. In addition, first nonfatal complications after index AMI and their associated mortality were analyzed as crude Kaplan–Meier curves and in age-adjusted Cox proportional hazard regression models, where patients with no event during follow-up served as a reference in order to further explore which event was the most fatal. A 2-sided *P* value of <0.05 was accepted as statistically significant. All analyses were conducted using the SPSS statistical program (SPSS, version 26) software from SPSS Inc, Chicago, IL.

Ethical Consideration

The study has been approved by the local ethics boards at the Karolinska Institute (DNR 2017/432-32) and Uppsala University (DNR 2011/333/5). No individual consent to enter the SWEDEHEART registry was obtained, but patients were informed about the opportunity to opt out. The study complies with the Declaration of Helsinki.

RESULTS

In all, 61 675 patients with AMI undergoing a coronary angiography and surviving the first 30 days were identified during the study period (Figure 1). We excluded patients with known diabetes (n=14 536; 24%) and patients without diagnosed diabetes with glucose levels of <2 mmol/L (36 mg/dL) and >11 mmol/L (198 mg/dL), resulting in n=45 468 patients.

Baseline Characteristics

The baseline characteristics in patients without diagnosed diabetes with glucose levels between 2.0 and 11.0 mmol/L (36–198 mg/dL; n=45 468) are presented in the Table by glucose level strata. The mean age was 68 (SD±12) years, 70% were male, and 22% had glucose levels between 7.8 and 11.0 mmol/L (140–198 mg/dL). Patients with higher glucose levels were older, more often female, and with an increased proportion of ST-segment–elevation myocardial infarction versus non–ST-segment–elevation myocardial infarction and somewhat more extensive coronary artery disease. Left ventricular ejection fraction (LVEF) evaluated at discharge was reported in 89% of the population. An LVEF of <50% was present in 35% and was more common in higher glucose levels. Apart from hypertension, there were only negligible differences in other comorbidities where the overall proportion of patients with previously recorded renal failure or HF was low (2% versus 4%).

Outcome

During a mean follow-up period of 3.3 (SD 1.7) years, 26% (n=11 623) had MACE and 9% (n=4034) of the patients died. A recurrent MI was reported in 13% (n=5717), stroke in 3% (n=1337), HF in 12% (n=5237), and renal failure in 4% (n=1987). When grouped together, 13% (n=6103) had cardiorenal events (HF *or* renal failure) and 15% (n=6731) had MI *or* stroke.

Details on cumulative event rates stratified by glucose strata are presented in Figure 2A through 2H illustrating a stepwise higher risk for MACE (Figure 2A), death (Figure 2B), and cardiorenal events (Figure 2D, 2F, 2G) in higher glucose strata. This pattern was not seen for a MI or stroke (Figure 2C, 2E, 2H).

Figure 3 depicts associated HR for different outcomes by glucose level strata in a Forest plot (extensive outcome data are presented in Table S1). Patients in the highest strata (7.8–11.0 mmol/L [140–198 mg/dL]) ran an increased risk of MACE (adjusted HR, 1.17 [95% CI, 1.11–1.23], *P*<0.001), HF (1.40; 1.30–1.51, *P*<0.001), renal failure (1.17; 1.04–1.33, *P*=0.009), and all-cause death (1.31; 1.20–1.43, *P*<0.001). No association between glucose strata and MI (0.99; 0.92–1.07, *P*=0.849) or stroke (1.03; 0.88–1.19, *P*=0.742) was observed. The association with HF and all-cause death was present regardless of LVEF (LVEF <50%: 1.28; 1.17–1.39, *P*<0.001 and LVEF ≥50%: 1.17; 1.04–1.30, *P*=0.007).

In restricted cubic spline analyses with glucose levels modeled as a continuous variable, increasing levels of glucose were associated with a higher risk of MACE (Figure 4A), in particular with cardiorenal events (Figure 4B and 4C) but less with atherothrombotic events (Figure 4D). In restricted cubic spline analyses of HbA1c (available in 23%), a similar pattern was seen (Figure S1A through S1D).

Figure 5 illustrates cumulative mortality rate after the first nonfatal clinical event after the index AMI. In Cox proportional hazards regression analyses, hospitalization for renal failure was associated with the highest mortality risk (age-adjusted HR, 4.93 [95% CI, 4.34–5.60], *P*<0.001), followed by HF (3.71; 3.41–4.04, *P*<0.001), stroke (3.39; 2.94–3.91, *P*<0.001), and MI (2.08; 1.88–2.30, *P*<0.001) where the group with no complications after the index AMI served as a reference.

DISCUSSION

In this nationwide analysis exploring the importance of glucose levels at the initial hospital phase of an AMI in patients without diagnosed diabetes, there are 3 major important findings. First, mildly elevated glucose levels identify individuals already at AMI hospitalization with an increased risk of long-term

Table. Patient Characteristics at Baseline, Median (Interquartile Range), or n (%), by Glucose (mmol/L) Level Strata

	n	Group I Glucose 2.0–3.9 mmol/L (36–71 mg/dL) (n=103)	Group II Glucose 4.0–6.0 mmol/L (72–109 mg/dL) (n=15 581)	Group III Glucose 6.1–6.9 mmol/L (110–125 mg/dL) (n=12 624)	Group IV Glucose 7.0–7.7 mmol/L (126–139 mg/dL) (n=7066)	Group V Glucose 7.8–11.0 mmol/L (140–198 mg/dL) (n=10 094)
Clinical characteristics						
Age, y	45 468	65 (47–83)	67 (50–84)	68 (52–84)	69 (53–85)	70 (54–86)
Sex (male)	45 468	76 (73.8)	11 091 (71.2)	8982 (71.2)	4926 (69.7)	6927 (68.6)
Current smoker	45 467	27 (26.2)	3836 (24.6)	2908 (23.0)	1588 (22.5)	2192 (21.7)
BMI, kg/m^2	44 559	24.7 (20.3–29.1)	26.0 (21.2–30.9)	26.5 (21.4–31.6)	26.6 (21.4–31.8)	26.5 (21.3–31.8)
Weight, kg	45 164	75 (58–92)	80 (61–99)	80 (60–100)	80 (60–100)	80 (60–100)
Killip class I	39 299	82 (97.6)	12 621 (97.4)	10 478 (96.7)	6031 (95.8)	8561 (93.9)
Previous disease						
Myocardial infarction	45 468	16 (15.5)	2230 (14.3)	1906 (15.1)	1058 (15.0)	1447 (14.3)
Heart failure	45 468	6 (5.8)	563 (3.6)	495 (3.9)	286 (4.0)	432 (4.3)
PAD	45 468	3 (2.9)	524 (3.4)	410 (3.2)	231 (3.3)	335 (3.3)
PCI	45 468	8 (7.8)	1733 (11.1)	1461 (11.6)	741 (10.5)	1070 (10.6)
CABG	45 468	6 (5.8)	727 (4.7)	578 (4.6)	327 (4.6)	407 (4.0)
Stroke	45 468	5 (4.9)	804 (5.2)	638 (5.1)	368 (5.2)	539 (5.3)
Renal failure	45 468	2 (1.9)	288 (1.8)	190 (1.5)	139 (2.0)	208 (2.1)
Cancer	45 468	3 (2.9)	330 (2.1)	287 (2.3)	143 (2.0)	230 (2.3)
Dementia	45 468	0 (0)	41 (0.3)	28 (0.2)	25 (0.4)	29 (0.3)
Hypertension	45 467	44 (42.7)	7281 (46.7)	6298 (49.9)	3468 (49.1)	5118 (50.7)
Hyperlipidemia	45 468	29 (28.2)	4816 (30.9)	3893 (30.8)	2060 (29.2)	2785 (27.6)
Biochemistry						
HbA1c, mmol/mol	10 464	37 (31–43)	37 (32–42)	38 (33–43)	38 (33–43)	39 (33–45)
HbA1c (%)	10 464	5.5 (5.0–6.1)	5.5 (5.1–6.0)	5.6 (5.2–6.1)	5.6 (5.2–6.1)	5.7 (5.2–6.3)
CRP, mg/L	43 334	5 (0–12)	4 (0–9)	4 (0–10)	4 (0–10)	4 (0–10)
Creatinine, mmol/L	45 292	83 (58–108)	79 (55–103)	79 (55–103)	79 (55–103)	80 (54–106)
Indication	45 468					
NSTEMI		60 (58.3)	10 882 (69.8)	7677 (60.8)	3713 (52.5)	4462 (44.2)
STEMI		43 (41.7)	4699 (30.2)	4947 (39.2)	3353 (47.5)	5632 (55.8)
Angiographic findings	45 464					
Normal		10 (9.7)	1340 (8.6)	978 (7.7)	428 (6.1)	583 (5.8)
1-vessel		42 (40.8)	7057 (45.3)	5670 (44.9)	3232 (45.8)	4500 (44.6)
2-vessel		27 (26.2)	3896 (25.0)	3213 (25.5)	1837 (26.0)	2682 (26.6)
3-vessel		18 (17.5)	2347 (15.1)	1987 (15.7)	1178 (16.7)	1669 (16.5)
Left main		6 (5.8)	918 (5.9)	761 (6.0)	380 (5.4)	649 (6.4)
Revascularization method						
PCI	45 468	78 (75.7)	12 726 (81.7)	10 453 (82.8)	6001 (84.9)	8717 (86.4)
CABG ≤3 mo after index AMI	45 468	3 (2.9)	162 (1.0)	119 (0.9)	64 (0.9)	83 (0.8)
Stent during PCI	37 975	71 (91.0)	11 495 (90.3)	9498 (90.9)	5481 (91.3)	8077 (92.7)
Complete revascularization	36 856	47 (61.8)	8566 (70.0)	6825 (67.2)	3819 (65.2)	5345 (62.6)
EF% at discharge	40 263					
EF ≥50%		66 (71.7)	9914 (72.0)	7383 (66.4)	3779 (60.4)	4911 (54.4)
EF 40%–49%		16 (17.4)	2469 (17.9)	2301 (20.7)	1441 (23.0)	2193 (24.3)
EF 30%–39%		8 (8.7)	1052 (7.6)	1090 (9.8)	764 (12.2)	1380 (15.3)
EF <30%		2 (2.2)	262 (1.9)	292 (2.6)	236 (3.8)	492 (5.5)

(*Continued*)

Table. Continued

	n	Group I Glucose 2.0–3.9 mmol/L (36–71 mg/dL) (n=103)	Group II Glucose 4.0–6.0 mmol/L (72–109 mg/dL) (n=15 581)	Group III Glucose 6.1–6.9 mmol/L (110–125 mg/dL) (n=12 624)	Group IV Glucose 7.0–7.7 mmol/L (126–139 mg/dL) (n=7066)	Group V Glucose 7.8–11.0 mmol/L (140–198 mg/dL) (n=10 094)
Unknown EF		0 (0)	82 (0.6)	51 (0.5)	34 (0.5)	45 (0.5)
Medications at discharge						
Aspirin	45 457	99 (96.1)	14 892 (95.6)	12 032 (95.3)	6696 (94.8)	9427 (93.4)
Clopidogrel	45 457	22 (21.4)	3526 (22.6)	2784 (22.1)	1545 (21.9)	2274 (22.5)
Ticagrelor	45 457	68 (66.0)	10 414 (66.9)	8604 (68.2)	4823 (68.3)	6900 (68.4)
β-Blockade	45 457	92 (89.3)	13 541 (86.9)	11 180 (88.6)	6336 (89.7)	9193 (91.1)
ACE inhibitor	45 457	59 (57.3)	9658 (62.0)	8037 (63.7)	4717 (66.7)	6667 (66.1)
Angiotensin II receptor inhibitor	45 451	19 (18.4)	2788 (17.9)	2454 (19.4)	1302 (18.4)	1964 (19.5)
Spironolactone	45 457	1 (1.0)	475 (3.0)	458 (3.6)	325 (4.6)	691 (6.8)
Eplerenone	45 457	0 (0)	153 (1.0)	171 (1.4)	126 (1.8)	201 (2.0)
Statin	45 457	95 (92.2)	14 955 (96.0)	12 160 (96.3)	6758 (95.7)	9597 (95.1)
Ezetemide	45 451	1 (1.0)	259 (1.7)	192 (1.5)	108 (1.5)	165 (1.6)

ACE inhibitor indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft; CRP, C-reactive protein; EF%, ejection fraction; HbAlc, hemoglobin A1c; NSTEMI, non–ST-segment–elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

complications. Second, the pattern of complications associated with mild dysglycemia was somewhat surprising and showed that this association was most apparent for cardiorenal complications, such as HF and renal failure, whereas there was no association observed for atherothrombotic events, such as MI and stroke. Third, hospitalization for HF and renal events post-MI were associated with the highest risk of subsequent mortality.

The present study extends previous knowledge on the associated risk between glucose levels and in-hospital mortality also to long-term mortality and cardiorenal complications, starting already at a lower degree of dysglycemia than previously reported.[23] This is illustrated in the restricted cubic spline analyses demonstrating a clear and continuous increasing risk of MACE already at glucose levels of ≤11 mmol/L (198 mg/dL), especially for both cardiorenal events and mortality. Surprisingly, this association was less evident for atherothrombotic events, such as stroke and MI. The same pattern with a continuous association, albeit not as evident, was also seen for HbA1c; however, this was only reported in 23%. The present study shows that in patients without diagnosed diabetes with glucose levels ≤11 mmol/L (198 mg/dL), there appears to be a gradually increasing risk. In the glucose range 7–11 mmol/L (140–198 mg/dL) there was an ≈30% increased risk of cardiorenal events and mortality compared with nondiabetes with normal glucose values.

Explanations of a higher complication rate by increasing glucose levels could, for instance, include a more extensive MI and a more compromised LVEF, with higher rates of circulating catecholamines and accordingly rising glucose levels. However, biomarkers associated with infarction size, such as troponins, are not obtainable in this study whereas LVEF at discharge was available in the majority of patients. Indeed, among those with higher glucose levels at admission, reduced LVEF was more common and they were accordingly prescribed more HF medications (ie, angiotensin-converting enzyme inhibitors, angiotensin II inhibitors, and mineral corticosteroid receptor antagonists). Of note, complete revascularization was achieved to the same extent in all glucose strata, and there was only a modest difference in the burden of coronary artery disease. Interestingly, the association with future adverse events was also present in the group with preserved LVEF, although more detailed information (such as wall motion score index, global systolic strain, or diastolic values) was not available.

Another explanation for a higher complication rate associated with elevated glucose levels could be the presence of unknown diabetes/prediabetes. Several studies have demonstrated that as many as 50% to 60% of all patients with an AMI have undiagnosed prediabetes/diabetes that can be detected with an oral glucose tolerance test in a stable stage.[8,9] Accordingly, admission glucose levels should not be regarded as a diagnostic tool for diabetes status but rather as useful for prognostic implications. In the present study, as many as 40% to 50% were previously diagnosed with hypertension, a condition associated with prediabetes and the metabolic syndrome.[24] Contributory mechanisms associated with

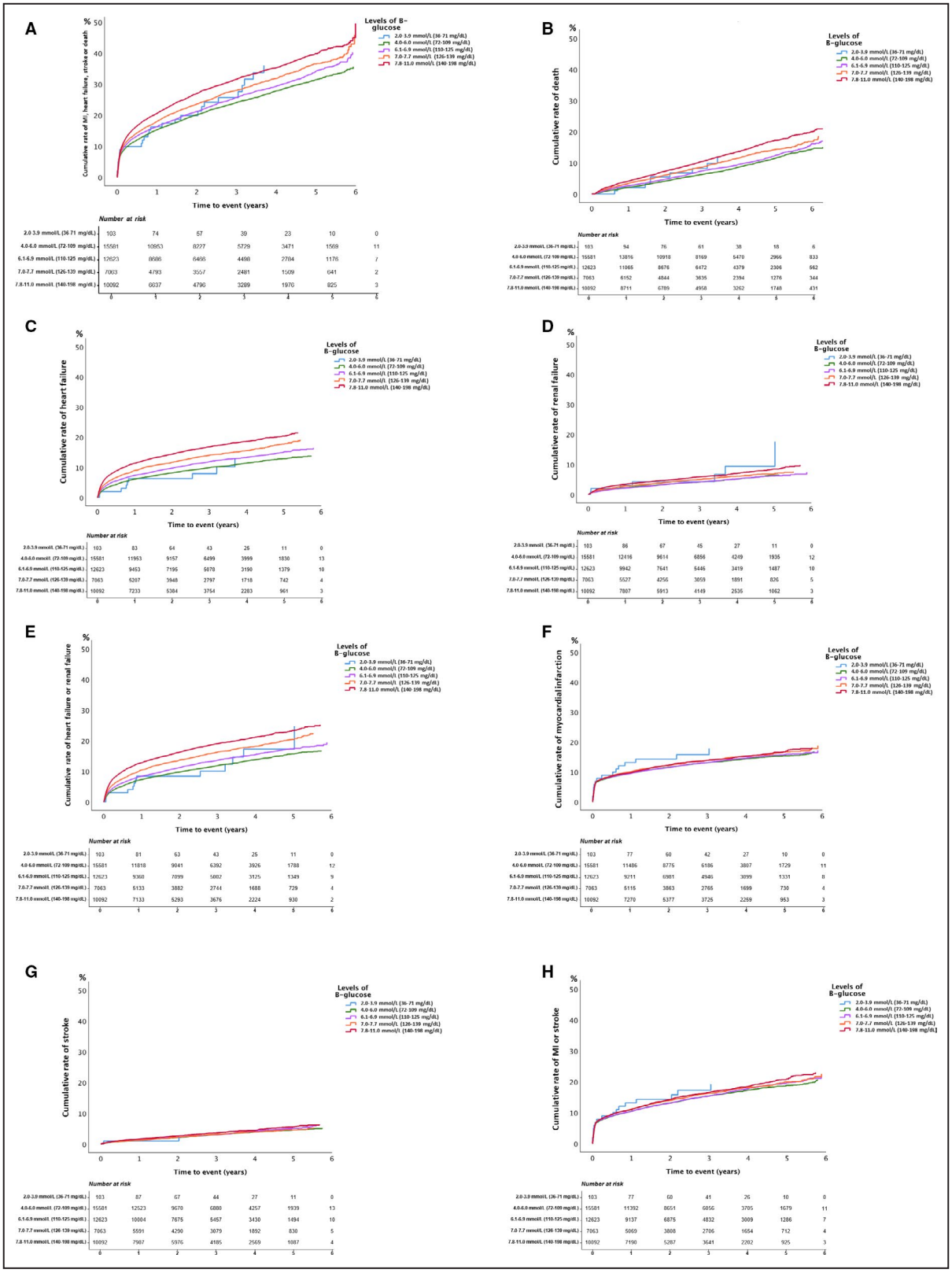

Figure 2. Time to hospitalization for major adverse cardiovascular events (A) after first occurrence of MI, heart failure, stroke, or death; (B) death; (C) heart failure; (D) renal failure; (E) heart failure/renal failure; (F) MI; (G) stroke; and (H) MI/stroke after index MI by glucose levels.

Patients who died during the first 30 days were excluded. MI indicates myocardial infarction.

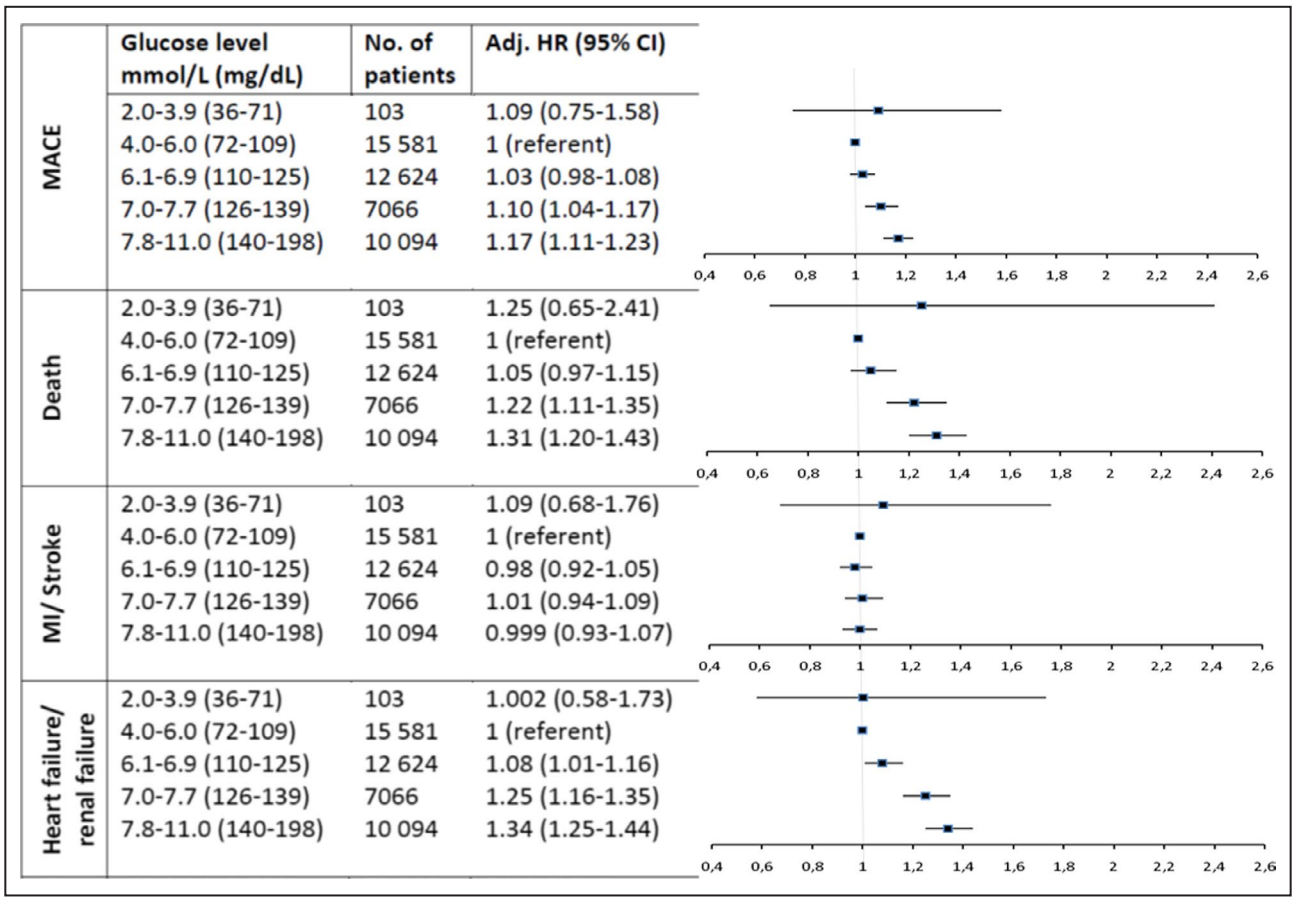

Figure 3. Adjusted associated HR (95% CI) for MACE (death, MI, stroke, or heart failure), death, MI /stroke, and heart failure/renal failure by glucose level strata.
Patients with blood glucose of 4–6 mmol/L (72–109 mg/dL) served as a reference group with HR 1.0. Extensive unadjusted and adjusted outcome data for single events are presented in Table S1. HR indicates hazard ratio; MACE, major adverse cardiovascular events; and MI, myocardial infarction.

increasing glucose levels include insulin resistance, cardiomyopathy as seen in diabetes, and adverse left ventricular remodeling and renal complications, such as microalbuminuria.[25,26]

In order to explore which event that was the most fatal regardless of glucose level, we analyzed the cumulative mortality rate after the first nonfatal event in an age-adjusted setting where the group without any event served as a reference. Despite only age adjustment, this is an interesting observation revealing the severe situation associated with renal and HF events. Renal events were associated with an almost 5-fold risk of mortality and HF with an almost 4-fold risk, although it is important to bear in mind that HF events were 3 times more common than renal events after MI.

In recent decades, treatment for preventing atherosclerotic events, such as platelet inhibitors, angiotensin-converting enzyme inhibitors, β-blockers, statins, and percutaneous coronary intervention with stent implantation, has been successfully introduced in a primary and secondary setting, whereas therapies and studies preventing HF and renal failure have been less common and less successful. Recently, studies of sodium-glucose co-transporter-2 inhibitors have revealed cardiorenal protective effects in patients with diabetes[27,28] and, regardless of diabetes, also in patients with HF and renal failure.[29–31] These findings have left a rapid legacy in several international guidelines and consensus documents, where the recent American Diabetes Association/European Association for the Study of Diabetes guidelines advocate the use of sodium-glucose co-transporter-2 inhibitors in patients with diabetes, if there is a dominant high risk of HF, and glucagon-like peptide-1 receptor antagonists, if there is a dominant risk of stroke and MI.[32–34] Our data demonstrating a high risk of cardiorenal events in those with mild hyperglycemia already identified at admission are interesting in this perspective, because they speculatively constitute an important possible new target group where sodium-glucose co-transporter-2 inhibitors or other agents

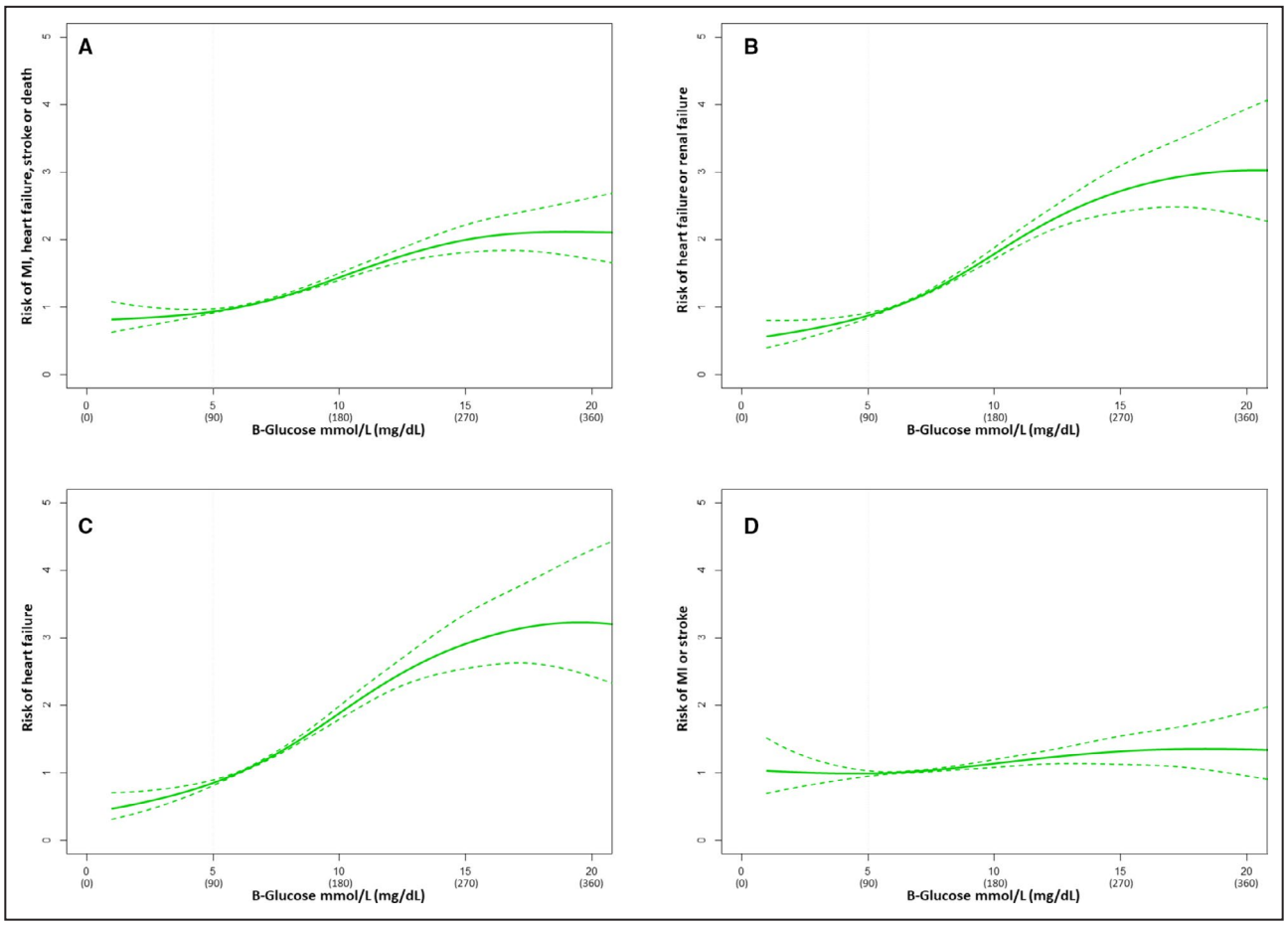

Figure 4. Restricted cubic spline analyses of association between continuous glucose level and (A) major adverse cardiovascular events, (B) heart failure or renal failure, (C) heart failure, and (D) MI or stroke.
The solid line demonstrates the hazard ratio (HR) and the dotted line the 95% CI. A glucose level of 5.0 mmol/L (90 mg/dL) served as a reference (HR, 1.0).

such as metformin (currently being investigated in the ongoing VA-IMPACT [Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular Outcomes] study[35]) could be suitable in order to prevent such cardiorenal complications in patients without diabetes.

Strengths and Limitations

A major strength of this study is the inclusion of a large number of patients with available glucose levels. Furthermore, the linkage of SWEDEHEART with highly validated national registries enabled a careful long-term follow-up with no patient lost during follow-up. Another strength is the inclusion of patients surviving 30 days, where death during hospitalization (for example, because of cardiogenic shock) or soon thereafter has been excluded. All patients underwent coronary angiography and a majority were judged to have a complete revascularization, which we believe is a strength rather than a limitation, resulting in a more homogeneous modern treated cohort. Data therefore cannot be extrapolated to those with a medically managed AMI. There is uncertainty about at what time point glucose is analyzed during the first day of hospitalization for AMI; however, the majority are most likely fasting glucose. Although access to HbA1c was limited (23% of the patients), the median HbA1c in all glucose groups was below the cut-off for diabetes (HbA1c 48; Diabetes Control and Complications Trial 6.5%), but with a few patients with HbA1c >6.5%, suggesting glucose disturbances/prediabetes at an early stage. The limitations of this register-based study include the possibility of unknown residual confounders that are impossible to control for and the lack of information on medications during follow-up. Information on subtype of HF (HF with preserved ejection fraction and HF with reduced ejection fraction) is not available. Another limitation is the lack of information on oral glucose tolerance test and the detection of undiagnosed diabetes during hospitalization and follow-up, because this information

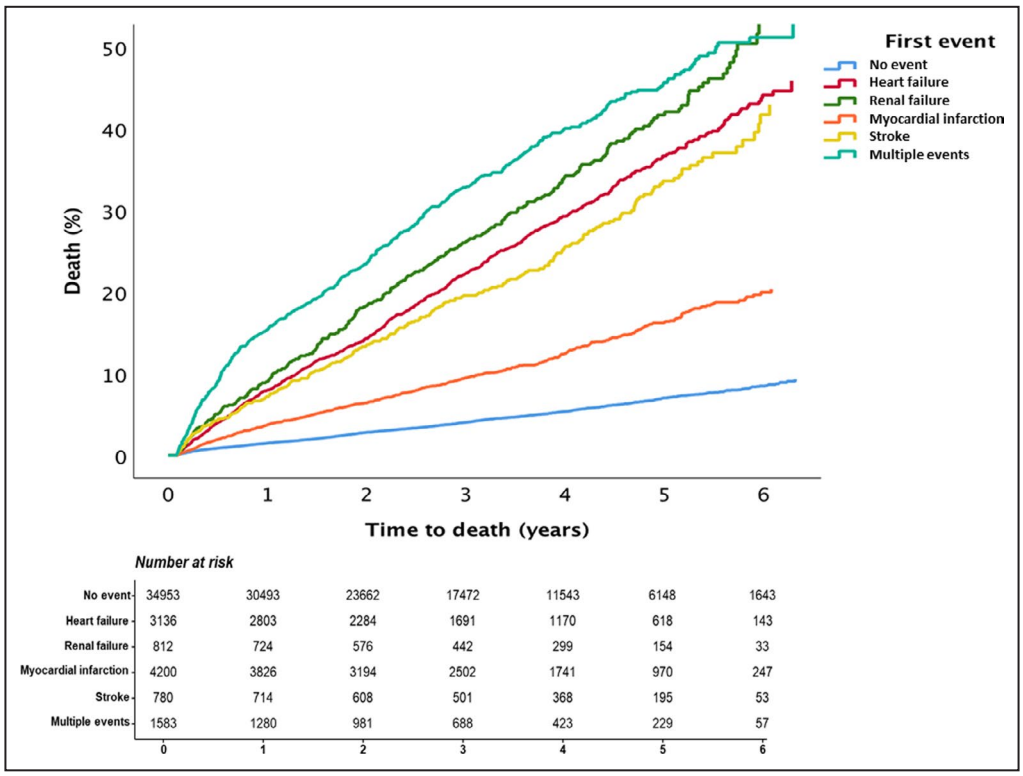

Figure 5. Time to mortality by first clinical event (heart failure, renal failure, stroke, or myocardial infarction) after index myocardial infarction.
Patients who died during the first 30 days were excluded. Multiple events was defined as several of these events during the same hospitalization.

is not compulsory in SWEDEHEART. Because of the detailed patient-level clinical phenotype with information on prior diabetes diagnoses and health record data, we were able to exclude patients with known diabetes, even excluding those with glucose levels of >11 mmol/L (198 mg/dL), a group in which the prevalence of diabetes is high. During follow-up, all-cause mortality was collected where cardiovascular death was not identified. Furthermore, renal failure was collected through *ICD-10* diagnoses, and there are no data on estimated glomerular filtration rate during follow-up, making a more precise determination of renal function impossible.

CONCLUSIONS

Mildly elevated admission glucose levels in patients without diagnosed diabetes with AMI identify individuals running an increased risk of long-term complications. This association was most apparent for cardiorenal events such as HF and renal failure while not obvious for atherothrombotic events, such as MI and stroke. Importantly, there was a sign of a higher and earlier mortality risk after such cardiorenal events. These results emphasize that glucose at admission should be considered as a risk marker of future major adverse events.

ARTICLE INFORMATION

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Disclosures

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Supplementary Material

Table S1
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Unadjusted and adjusted risk (HR CI 95%) of events after index myocardial infarction in patients stratified by glucose levels mmol/L (mg/dL). Patients with blood glucose of 4-6 mmol/L (72-109 mg/dL) served as a reference group with HR 1.0.

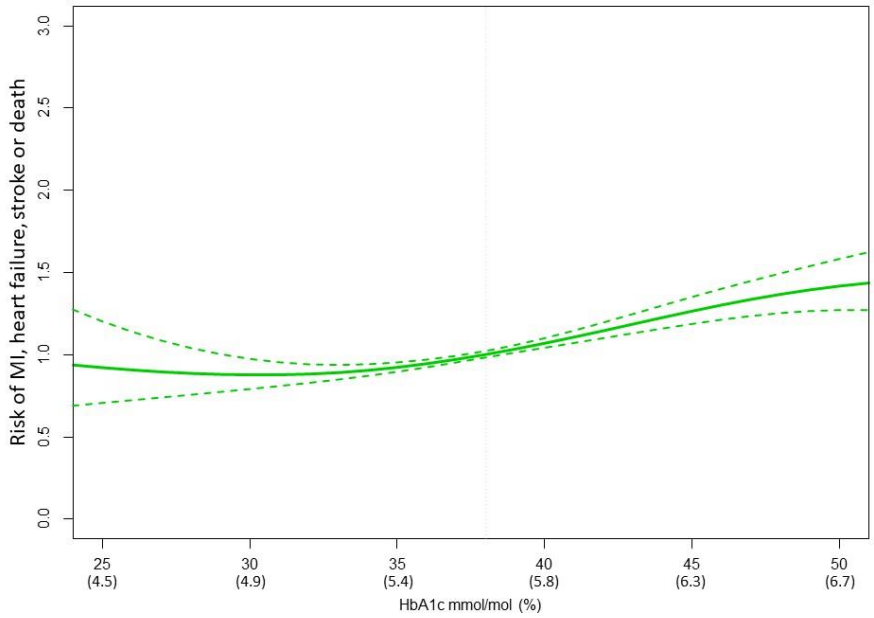
Event	Events n (%)	Unadjusted HR (95% CI)	p-value	Adjusted* HR (95%CI)	p-value
MI, heart failure, stroke, death	11623 (25.6)				
Glucose 2.0-3.9 (36-71)	28 (27.2)	1.16 (0.80-1.69)	0.423	1.09 (0.75-1.58)	0.752
Glucose 4.0-6.0 (72-109)	3594 (23.1)	1 (referent)		1 (referent)	
Glucose 6.1-6.9 (110-125)	3100 (24.6)	1.09 (1.04-1.14)	0.001	1.03 (0.98-1.08)	0.231
Glucose 7.0-7.7 (126-139)	1896 (26.8)	1.20 (1.13-1.27)	<0.001	1.10 (1.04-1.17)	0.001
Glucose 7.8-11.0 (140-198)	3005 (29.8)	1.37 (1.30-1.44)	<0.001	1.17 (1.11-1.23)	<0.001
Mortality	4034 (8.9)				
Glucose 2.0-3.9 (36-71)	9 (8.7)	1.16 (0.60-2.23)	0.667	1.25 (0.65-2.41)	0.510
Glucose 4.0-6.0 (72-109)	1154 (7.4)	1 (referent)		1 (referent)	
Glucose 6.1-6.9 (110-125)	1030 (8.2)	1.12 (1.03-1.22)	0.008	1.05 (0.97-1.15)	0.246
Glucose 7.0-7.7 (126-139)	684 (9.7)	1.34 (1.22-1.47)	<0.001	1.22 (1.11-1.35)	<0.001
Glucose 7.8-11.0 (140-198)	1157 (11.5)	1.62 (1.49-1.76)	<0.001	1.31 (1.20-1.43)	<0.001
Heart failure	5237 (11.5)				
Glucose 2.0-3.9 (36-71)	9 (8.7)	0.93 (0.48-1.79)	0.823	0.81 (0.42-1.55)	0.518
Glucose 4.0-6.0 (72-109)	1424 (9.1)	1 (referent)		1 (referent)	
Glucose 6.1-6.9 (110-125)	1358 (10.8)	1.20 (1.12-1.29)	<0.001	1.12 (1.04-1.20)	0.004
Glucose 7.0-7.7 (126-139)	903 (12.8)	1.45 (1.33-1.57)	<0.001	1.26 (1.16-1.38)	<0.001
Glucose 7.8-11.0 (140-198)	1543 (15.3)	1.78 (1.65-1.91)	<0.001	1.40 (1.30-1.51)	<0.001
Renal failure	1987 (4.4)				
Glucose 2.0-3.9 (36-71)	7 (6.8)	1.68 (0.80-3.53)	0.174	1.82 (0.86-3.84)	0.117
Glucose 4.0-6.0 (72-109)	619 (4.0)	1 (referent)		1 (referent)	
Glucose 6.1-6.9 (110-125)	490 (3.9)	0.99 (0.88-1.11)	0.861	0.99 (0.88-1.12)	0.888
Glucose 7.0-7.7 (126-139)	324 (4.6)	1.18 (1.03-1.34)	0.019	1.15 (1.00-1.32)	0.049
Glucose 7.8-11.0 (140-198)	547 (5.4)	1.42 (1.26-1.59)	<0.001	1.17 (1.04-1.33)	0.009
Myocardial infarction	5717 (12.6)				
Glucose 2.0-3.9 (36-71)	16 (15.5)	1.26 (0.77-2.06)	0.361	1.19 (0.73-1.95)	0.488
Glucose 4.0-6.0 (72-109)	1919 (12.3)	1 (referent)		1 (referent)	
Glucose 6.1-6.9 (110-125)	1563 (12.4)	1.01 (0.95-1.08)	0.694	0.98 (0.92-1.05)	0.528
Glucose 7.0-7.7 (126-139)	919 (13.0)	1.07 (0.99-1.16)	0.100	1.02 (0.94-1.11)	0.586
Glucose 7.8-11.0 (140-198)	1300 (12.9)	1.07 (0.995-1.15)	0.071	0.99 (0.92-1.07)	0.849
Stroke	1337 (2.9)				
Glucose 2.0-3.9 (36-71)	2 (1.9)	0.68 (0.17-2.74)	0.590	0.73 (1.82-2.93)	0.658
Glucose 4.0-6.0 (72-109)	433 (2.8)	1 (referent)		1 (referent)	
Glucose 6.1-6.9 (110-125)	373 (3.0)	1.08 (0.94-1.24)	0.273	1.03 (0.89-1.18)	0.724
Glucose 7.0-7.7 (126-139)	197 (2.8)	1.02 (0.86-1.21)	0.798	0.95 (0.80-1.13)	0.546
Glucose 7.8-11.0 (140-198)	332 (3.3)	1.23 (1.07-1.42)	0.004	1.03 (0.88-1.19)	0.742
Heart failure, renal failure	6103 (13.4)				
Glucose 2.0-3.9 (36-71)	13 (12.6)	1.11 (0.65-1.92)	0.702	1.002 (0.58-1.73)	0.994
Glucose 4.0-6.0 (72-109)	1719 (11.0)	1 (referent)		1 (referent)	
Glucose 6.1-6.9 (110-125)	1566 (12.4)	1.15 (1.07-1.23)	<0.001	1.08 (1.01-1.16)	0.025
Glucose 7.0-7.7 (126-139)	1052 (14.9)	1.40 (1.29-1.51)	<0.001	1.25 (1.16-1.35)	<0.001
Glucose 7.8-11.0 (140-198)	1753 (17.4)	1.68 (1.57-1.79)	<0.001	1.34 (1.25-1.44)	<0.001
Heart failure, renal failure, death	8163 (18.0)				
Glucose 2.0-3.9 (36-71)	17 (16.5)	1.07 (0.67-1.73)	0.771	0.997 (0.62-1.61)	0.990

Glucose 4.0-6.0 (72-109)	2328 (14.9)	1 (referent)		1 (referent)	
Glucose 6.1-6.9 (110-125)	2113 (16.7)	1.15 (1.08-1.22)	<0.001	1.08 (1.01-1.14)	0.018
Glucose 7.0-7.7 (126-139)	1403 (19.9)	1.38 (1.29-1.48)	<0.001	1.25 (1.16-1.33)	<0.001
Glucose 7.8-11.0 (140-198)	2302 (22.8)	1.64 (1.55-1.74)	<0.001	1.31 (1.23-1.39)	<0.001
Heart failure, death	7558 (16.6)				
Glucose 2.0-3.9 (36-71)	15 (14.6)	1.04 (0.63-1.73)	0.885	0.96 (0.58-1.59)	0.871
Glucose 4.0-6.0 (72-109)	2120 (13.6)	1 (referent)		1 (referent)	
Glucose 6.1-6.9 (110-125)	1965 (15.6)	1.17 (1.10-1.25)	<0.001	1.09 (1.02-1.16)	0.007
Glucose 7.0-7.7 (126-139)	1305 (18.5)	1.41 (1.32-1.51)	<0.001	1.26 (1.17-1.35)	<0.001
Glucose 7.8-11.0 (140-198)	2153 (21.3)	1.69 (1.59-1.79)	<0.001	1.33 (1.25-1.42)	<0.001
Myocardial infarction, stroke	6731 (14.8)				
Glucose 2.0-3.9 (36-71)	17 (16.5)	1.13 (0.70-1.83)	0.605	1.09 (0.68-1.76)	0.717
Glucose 4.0-6.0 (72-109)	2248 (14.4)	1 (referent)		1 (referent)	
Glucose 6.1-6.9 (110-125)	1844 (14.6)	1.02 (0.96-1.09)	0.485	0.98 (0.92-1.05)	0.599
Glucose 7.0-7.7 (126-139)	1068 (15.1)	1.06 (0.99-1.14)	0.106	1.01 (0.94-1.09)	0.776
Glucose 7.8-11.0 (140-198)	1554 (15.4)	1.10 (1.03-1.17)	0.006	0.999 (0.93-1.07)	0.977
Myocardial infarction, stroke, death	9378 (20.6)				
Glucose 2.0-3.9 (36-71)	22 (21.4)	1.10 (0.72-1.67)	0.664	1.06 (0.70-1.61)	0.790
Glucose 4.0-6.0 (72-109)	2992 (19.2)	1 (referent)		1 (referent)	
Glucose 6.1-6.9 (110-125)	2491 (19.7)	1.04 (0.99-1.10)	0.142	0.996 (0.94-1.05)	0.884
Glucose 7.0-7.7 (126-139)	1520 (21.5)	1.14 (1.07-1.21)	<0.001	1.07 (1.01-1.14)	0.031
Glucose 7.8-11.0 (140-198)	2353 (23.3)	1.26 (1.19-1.33)	<0.001	1.10 (1.04-1.17)	0.001
Heart failure, death in EF ≥ 50%	2440 (5.4)				
Glucose 2.0-3.9 (36-71)	4 (3.9)	0.72 (0.27-1.91)	0.505	0.81 (0.30-2.17)	0.676
Glucose 4.0-6.0 (72-109)	814 (5.2)	1 (referent)		1 (referent)	
Glucose 6.1-6.9 (110-125)	668 (5.3)	1.13 (1.02-1.25)	0.023	1.08 (0.98-1.20)	0.131
Glucose 7.0-7.7 (126-139)	399 (5.6)	1.31 (1.16-1.47)	<0.001	1.18 (1.05-1.34)	0.007
Glucose 7.8-11.0 (140-198)	555 (5.5)	1.44 (1.29-1.60)	<0.001	1.17 (1.04-1.30)	0.007
Heart failure, death in EF < 50%	4143 (9.1)				
Glucose 2.0-3.9 (36-71)	9 (8.7)	1.23 (0.64-2.36)	0.544	0.99 (0.51-1.92)	0.976
Glucose 4.0-6.0 (72-109)	1004 (6.4)	1 (referent)		1 (referent)	
Glucose 6.1-6.9 (110-125)	999 (7.9)	1.04 (0.96-1.14)	0.336	1.02 (0.94-1.12)	0.606
Glucose 7.0-7.7 (126-139)	758 (10.7)	1.23 (1.12-1.35)	<0.001	1.21 (1.10-1.33)	<0.001
Glucose 7.8-11.0 (140-198)	1373 (13.6)	1.38 (1.27-1.50)	<0.001	1.28 (1.17-1.39)	<0.001

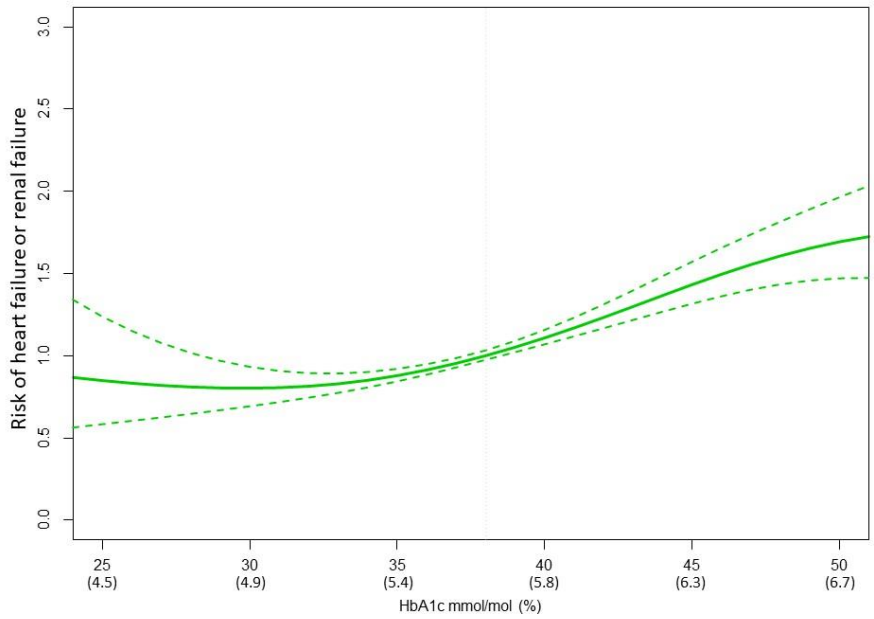
* Adjusted for age, sex, smoking, creatinine, previous diagnosis of myocardial infarction/heart failure/CABG/cancer/dementia/dialysis/hypertension/chronic obstructive pulmonary disease/renal failure/stroke/peripheral arterial disease, year, indication, hospital, angiographic findings, primary decision after angiography, cardiac chock and medications at discharge (ACE inhibitors, angiotensin II receptor antagonists, lipid-lowering agents, aspirin, beta blockade, oral anticoagulants, other antiplatelet therapy)

Figure S1. Restricted cubic spline analyses of association between continuous HbA1c and (A) MACE (B) heart failure or renal failure, (C) heart failure and (D) MI or stroke. The solid line demonstrates the hazard ratio (HR) and the dotted line the 95% confidence interval. HbA1c 38 mmol/mol (5.6%) served as a reference (HR 1.0).

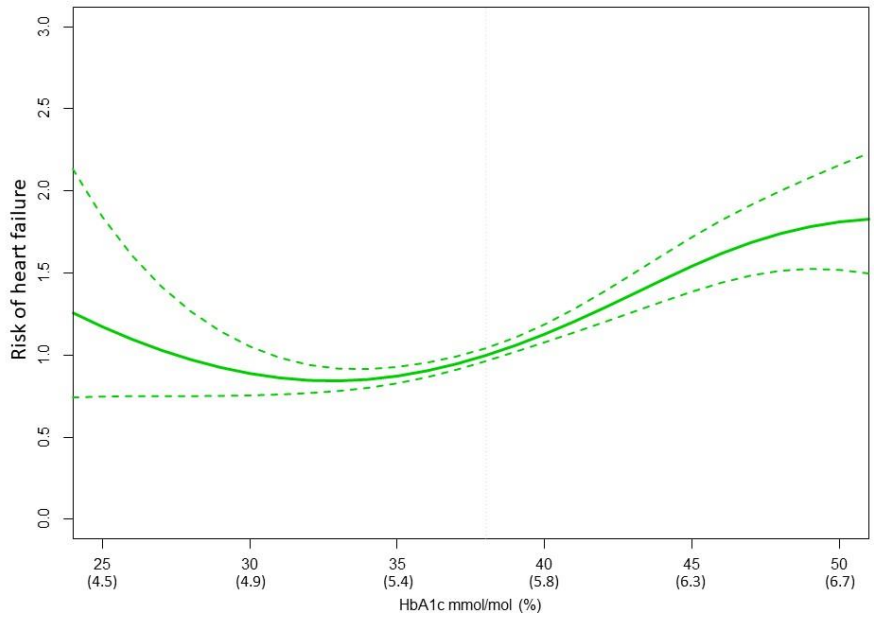
A.



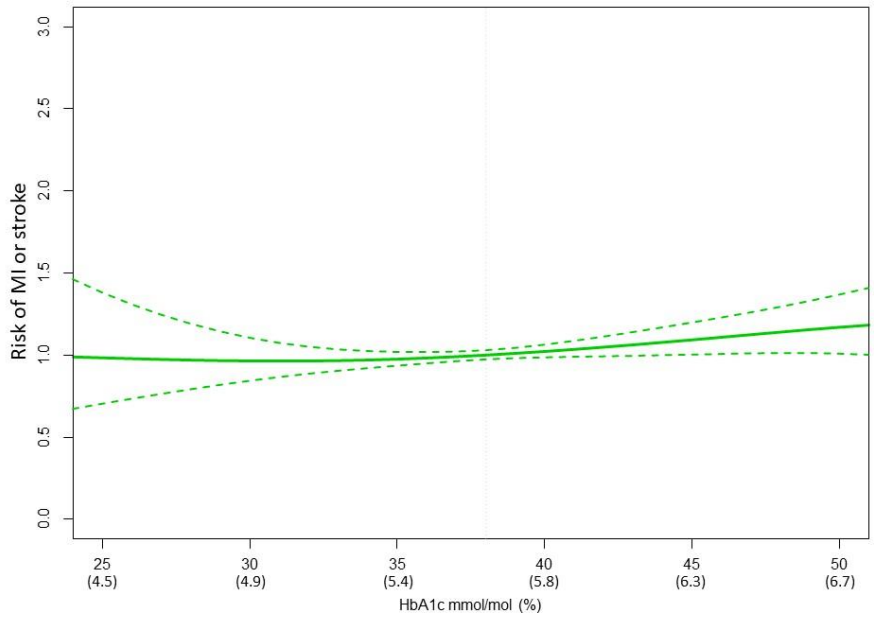
B.



C.


Risk of heart failure
0.0
0.5
1.0
1.5
2.0
2.5
3.0
25 (4.5)
30 (4.9)
35 (5.4)
40 (5.8)
45 (6.3)
50 (6.7)
HbA1c mmol/mol (%)

D.


Risk of MI or stroke
0.0
0.5
1.0
1.5
2.0
2.5
3.0
25 (4.5)
30 (4.9)
35 (5.4)
40 (5.8)
45 (6.3)
50 (6.7)
HbA1c mmol/mol (%)