One-Year Mortality in Elderly Adults with Non-ST-Elevation Acute Coronary Syndrome: Effect of Diabetic Status and Admission Hyperglycemia

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OBJECTIVES: To determine whether type 2 diabetes mellitus and hyperglycemia on admission should be considered independent predictors of mortality in elderly adults with acute coronary syndrome (ACS).

DESIGN: Prospective cohort study.

SETTING: Twenty-three hospitals in Italy.

PARTICIPANTS: Individuals aged 75 and older with non-ST-elevation ACS (NSTEACS) (mean age 82, 47% female) (N = 645).

MEASUREMENTS: Diabetic status and blood glucose levels were assessed on admission. Hyperglycemia was defined as glucose greater than 140 mg/dL. Multivariable Cox proportional hazard regression was used to assess the potential confounding effect of major covariates on the association between diabetic status, admission glucose, and 1-year mortality.

RESULTS: A history of diabetes mellitus was found in 231 participants (35.8%), whereas 257 (39.8%) had hyperglycemia. Hyperglycemia was found in 171 participants with diabetes mellitus (70%) and 86 (21%) without diabetes mellitus. Participants with diabetes mellitus were significantly ($P < .05$) more likely to have had prior myocardial infarction and stroke and had lower ejection fraction and blood hemoglobin. Hyperglycemia was associated with lower ($P < .05$) ejection fraction and estimated glomerular filtration rate (eGFR). Diabetic status and hyperglycemia were associated with greater 1-year mortality according to univariate analysis (54 participants with diabetes mellitus died (23.4%), versus 66 (15.9%) without diabetes mellitus (hazard ratio (HR) = 1.5 95% confidence interval (CI) = 1.0–2.1), and 60 participants with hyperglycemia died (23.3%), versus 60 (15.5%) without hyperglycemia (HR=1.6; 95% CI = 1.1–2.2), but this association was not statistically significant after adjustment for ejection fraction, age, blood hemoglobin, and eGFR.

CONCLUSION: In elderly adults with NSTEACS, diabetes mellitus and hyperglycemia on admission are associated with higher mortality, mostly because of preexisting cardiovascular and renal damage. **J Am Geriatr Soc 2014.**

Key words: acute coronary syndrome; diabetes mellitus; hyperglycemia; mortality; elderly

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Clinical Trial Registration—NCT 00510185, ClinicalTrials.gov.

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Diabetes mellitus is an independent predictor of mortality in individuals with non-ST-elevation acute coronary syndromes (NSTEACS).[1–3] Individuals with ACS with diabetes mellitus have more-extensive coronary artery disease, more-severe myocardial dysfunction, and more comorbidities than those with ACS without diabetes mellitus, which explains the higher mortality. A number of reports have also shown that, regardless of diabetic status, high plasma glucose concentration at the time of admission for ACS is associated with greater risk of in-hospital and long-term mortality,[4–8] although whether the prognostic effect of diabetic status and hyperglycemia on admission holds true in elderly adults with NSTEACS, who have significant

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comorbidities and prior cardiovascular events, is still ill defined. A large retrospective analysis of individuals aged 65 and older with myocardial infarction (MI) hospitalized between 1994 and 1996 found that hyperglycemia on admission is associated with greater 30-day and 1-year mortality, especially in individuals without known diabetes mellitus.[9] This relationship persisted after correction for comorbidities and baseline characteristics.

The Italian Elderly ACS Study offers a unique opportunity to gain further information on these issues because it enrolled a prospective population of individuals aged 75 and older with NSTEACS.[10]

METHODS

Study Design and Participants

The Italian Elderly ACS study enrolled individuals aged 75 and older with NSTEACS admitted to 23 participating hospitals within 48 hours of the most-recent ischemic symptoms and showing ischemic electrocardiographic changes or high cardiac markers. Details of the study design, setting, and population have been published.[11] In brief, 313 participants were randomly assigned to an early invasive strategy with coronary angiography and possible revascularization or an initially conservative strategy with angiography only in the case of recurrent ischemic symptoms. The main exclusion criteria from enrollment in the randomized trial were secondary causes of ischemia, ongoing myocardial ischemia or heart failure despite optimized therapy, any myocardial revascularization or a cerebrovascular accident within 30 days before admission, serum creatinine greater than 2.5 mg/dL, any transfusions or bleeding within 6 weeks before admission, platelet count of less than 90,000 cells/μL, ongoing oral anticoagulation, severe obstructive lung disease, malignancy, or neurological deficit limiting follow-up.[10] The 332 individuals meeting the inclusion criteria for the study but excluded from the randomized trial for any reason were enrolled in a parallel registry and given usual care. Informed consent was a prerequisite for enrollment in the randomized trial and in the Registry. Follow-up visits were planned at 1, 6, and 12 months after discharge, with similar electronic case report forms for the trial and the registry. Upon admission, each investigator classified the individual as diabetic if the medical records contained documentation of a previous history of diabetes mellitus, use of an oral glucose-lowering medication or insulin, or a diagnosis of diabetes mellitus made on admission. Blood glucose levels were measured upon admission in the local laboratory at each participating center. Hyperglycemia was defined according to the American Diabetes Association (ADA) consensus definition as any in-hospital blood glucose of greater than 140 mg/dL.[12]

Study Outcome and Definitions

The primary aim of the present analysis was to investigate the effect of diabetic status and basal glycemia on 1-year mortality. The secondary endpoint was to evaluate the effect of the above-mentioned covariates on the 1-year composite endpoint of overall death, MI, stroke, and rehospitalization for cardiovascular causes. It was not attempted to include glycated hemoglobin on admission because it was not measured in all participants, and assays were not standard across laboratories. An independent event adjudication committee adjudicated the clinical events, and causes of death were adjudicated according to standard definitions, as previously published.[13]

Statistical Analysis

Continuous variables are described as means and standard deviations, and frequencies and proportions are reported for categorical variables. Chi-square or Fisher exact tests were used for categorical variables and the Student *t*-test for numerical variables. Multivariable Cox proportional hazards regression was used to assess the potential confounding effect of major covariates on the association between diabetic status, glycemia on admission, and the primary and secondary endpoints studied. Participant characteristics considered prognostically important based on the available literature and all covariates identified in the univariable analyses as being associated with follow-up events were entered into the models. Variables for inclusion were carefully chosen, given the number of follow-up events, to ensure parsimony of the final models. Only covariates available before or upon admission were considered as potential predictors. Before the analysis was performed, the proportional hazards of the survival probability curves were verified using a graphical check. Given previous findings that the nature of the association between high glucose levels and outcomes differs in individuals with and without diabetes mellitus,[9,14–16] participants were further classified into four groups: without diabetes mellitus and normoglycemic, without known diabetes mellitus but with hyperglycemia on admission, with a history of diabetes mellitus but without hyperglycemia, with diabetes mellitus and hyperglycemia. A dummy variable was created and entered in the analysis. Analyses were also repeated by modeling glucose levels as a continuous variable to assess 1-year primary and secondary endpoints in participants with and without recognized diabetes mellitus. The effect of the interactions of the variables included in the regression model with age was evaluated. The final model was adjusted for the participants being enrolled in the trial or included in the registry. Cumulative crude event rates were estimated for 1-year mortality and reported separately in relation to hyperglycemia on admission and diabetic status. The statistical analysis was performed using SPSS software, version 19.0 (SPSS, Inc., Chicago, IL).

RESULTS

Six hundred forty-five participants were enrolled: 313 in the randomized trial and 332 in the registry. Two hundred thirty-one participants were defined as having diabetes mellitus upon admission (35.9%), and 257 had hyperglycemia (39.8%). Hyperglycemia was associated with known diabetes mellitus in 171 participants (66% of participants with high blood glucose on admission) but was also observed in 86 (21%) participants without known diabetes mellitus. Of the participants classified as having diabetes

mellitus, 11% were on dietary treatment, 34% on insulin therapy, and 55% on oral glucose-lowering medications.

Baseline characteristics of the participants subdivided according to diabetic status and hyperglycemia upon admission are described in Table 1. (Table S1 shows the baseline characteristics according to the four mutually exclusive categories of diabetes mellitus and glycemia status.) Mean age and sex were similar in participants with and without diabetes mellitus, whereas participants with diabetes mellitus had a longer history of prior cardiovascular events, including MI, heart failure, and stroke; ejection fraction and hemoglobin levels were lower in participants with diabetes mellitus, whereas glycosylated hemoglobin levels were higher. There were no differences related to concomitant medications during hospitalization, procedures performed, or drugs prescribed at discharge. Length of hospital stay was significantly longer in participants with diabetes mellitus (Table 2).

Hyperglycemia on admission was associated with lower estimated glomerular filtration rate (eGFR) and lower ejection fraction. Coronary angiography was slightly less frequently performed and aspirin less often prescribed at discharge in participants with hyperglycemia (Table 2).

Vital status at the end of follow-up was known for 98.3% of participants. Participants with diabetes mellitus had nonsignificantly higher rates of in-hospital death (6.1% vs 4.3%; hazard ratio (HR) = 1.4, 95% confidence interval (CI) = 0.7–2.8; $P = .37$) and cardiac events (death, MI, and stroke) ($P = .24$) (Figure S1A). At 1 year, mortality was significantly higher in participants with diabetes mellitus ($P = .03$ logrank) (Figure 1A), whereas the aggregate of death, MI, stroke, and repeated admission because of cardiovascular events did not differ ($P = .16$) according to diabetes status (Figure S1A). The adjudicated causes of death within the follow-up period were cardiovascular in 81% of participants with diabetes mellitus and 87% of those with no known diabetes mellitus.

Participants with hyperglycemia on admission had nonsignificantly higher in-hospital mortality (5.4% vs 4.6%; HR = 1.2; 95% CI = 0.6–2.4; $P = .64$) and cardiac events ($P = .33$) (Figure S1B). At 1 year, mortality was significantly higher ($P = .01$ logrank) in participants with hyperglycemia (Figure 1B), whereas composite events were nonsignificantly different ($P = .10$) (Figure S1B). The causes of death within the follow-up period were cardiovascular in 78% of the participants with

Table 1. Baseline Characteristics of the Study Population Stratified According to Diabetic Status and Glycemia on Admission

Characteristic	Overall, N = 645	Participants with Diabetes Mellitus, n = 231	Participants without Diabetes Mellitus, n = 414	*P*-Value	Participants with Hyperglycemia at Admission, n = 257	Participants without Hyperglycemia at Admission, n = 388	*P*-Value
Age, mean ± SD	81.6 ± 4.8	81.1 ± 4.47	81.9 ± 4.9	.02	81.7 ± 4.7	81.6 ± 4.8	.68
Male, n (%)	344 (53.3)	125 (54.1)	219 (52.9)	.76	135 (52.5)	209 (53.9)	.74
Estimated glomerular filtration rate, mean ± SD[a]	48.5 ± 19.5	47.4 ± 21.1	49.1 ± 18.6	.30	46.1 ± 20.1	50.1 ± 19.0	.01
Hypertension, n (%)	533 (82.7)	203 (87.7)	331 (79.9)	.22	219 (85.4)	314 (80.9)	.20
Atrial fibrillation, n (%)	87 (13.5)	38 (16.5)	49 (11.8)	.10	41 (16.0)	46 (11.9)	.13
Prior myocardial infarction, n (%)	200 (31.0)	89 (38.6)	111 (26.8)	.03	89 (34.6)	111 (28.6)	.15
Prior heart failure, n (%)	62 (9.6)	31 (13.2)	31 (7.5)	.09	26 (10.0)	36 (9.3)	.69
Prior percutaneous coronary intervention, n (%)	97 (15.0)	34 (14.9)	63 (15.1)	.90	42 (16.2)	55 (14.2)	.63
Prior coronary artery bypass grafting, n (%)	60 (9.3)	26 (11.4)	34 (8.2)	.58	24 (9.2)	36 (9.3)	.71
Prior stroke, n (%)	58 (9.0)	28 (12.1)	30 (7.2)	.03	25 (9.7)	33 (8.5)	.59
Elevated troponin levels, n (%)	483 (74.9)	168 (72.7)	315 (76.1)	.34	192 (74.7)	291 (75.0)	.93
Electrocardiographic ischemic changes, n (%)	506 (78.4)	188 (81.4)	318 (76.8)	.17	209 (81.3)	297 (76.5)	.15
Ejection fraction, mean ± SD	47.4 ± 10.9	45.3 ± 10.4	48.6 ± 11.1	<.01	44.7 ± 11.1	49.2 ± 10.4	<.01
Glycosylated hemoglobin,% (mmol/mol), mean ± SD[b]	5.7 ± 2.6	6.6 ± 2.8	5.0 ± 2.1	.01	6.2 ± 2.8	5.2 ± 2.2	.10
Hemoglobin, mean ± SD	12.9 ± 1.8	12.6 ± 2.1	13.1 ± 1.7	<.01	12.9 ± 2.0	12.9 ± 1.7	.97
Trial, n (%)							
Invasive	154 (23.9)	55 (23.8)	99 (23.9)	.92	66 (25.7)	88 (22.7)	.62
Conservative	159 (24.7)	59 (25.5)	100 (24.2)		64 (24.9)	95 (24.5)	
Registry	332 (51.5)	117 (50.6)	215 (51.9)		127 (49.4)	205 (52.8)	

[a] Using the Cockroft-Gault formula.

SD = standard deviation.

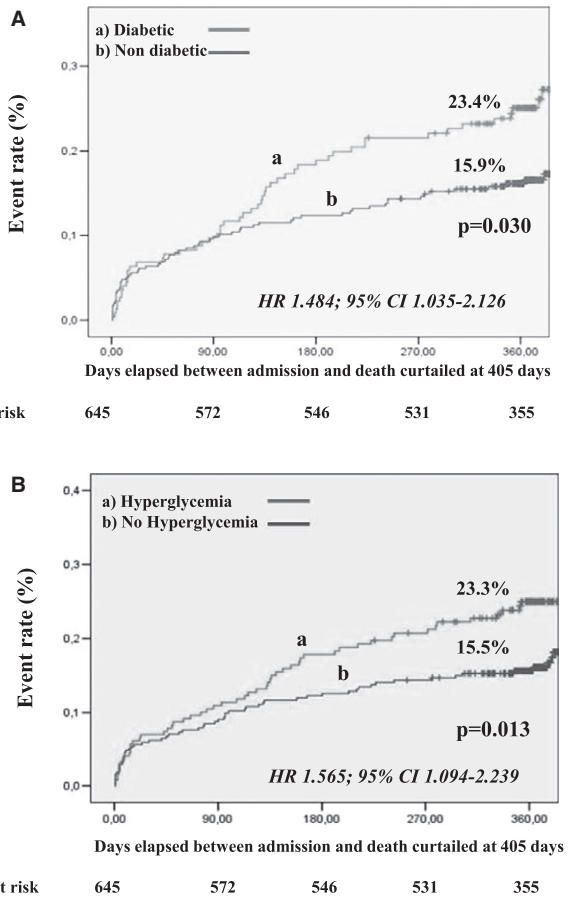

Figure 1. Cumulative crude risk of all-cause mortality in relation to diabetic status (**A**) and hyperglycemia on admission (**B**) after up to 405 days of follow-up. HR = hazard ratio; CI = confidence interval.

hyperglycemia and 83% of those without hyperglycemia on admission.

Figure 2 shows 1-year mortality risk curves according to the four mutually exclusive categories of diabetes mellitus and glycemia. Participants with diabetes mellitus, hyperglycemia, or both had greater risk of 1-year mortality according to univariable Cox regression analysis than participants without diabetes mellitus or hyperglycemia on admission (Table 3), although this greater risk of death was not statistically significant after adjustment for more-powerful predictors upon multivariable analysis, such as ejection fraction, age, blood hemoglobin, and eGFR. The above-mentioned analyses did not change when different cutoff values (180 or 200 mg/dL) for hyperglycemia were used. (Table S2 shows the multivariable model including diabetes mellitus and hyperglycemia as covariates).

With regard to the composite cardiovascular endpoint, neither diabetic status nor hyperglycemia (even in combination) was a predictor of cardiac events at 1 year. After stratification for diabetic status, hyperglycemia on admission was associated with a trend for a greater rate of cardiovascular events in participants without known diabetes mellitus (33/86 participants (38.3%) vs 61/171 (35.6%); HR = 1.4, 95% CI = 0.9–2.2, *P* for interaction = .45)). After adjustment for the most relevant covariates, only low ejection fraction, low hemoglobin level, age, and male

Table 2. Selected Cardiac Procedures and Medications During Index Admission and at Discharge According to Diabetic Status and Glycemia on Admission

Procedures and Medications	Overall, N = 645	Participants with Diabetes Mellitus, n = 231	Participants without Diabetes Mellitus, n = 414	*P*-Value	Participants with Hyperglycemia at Admission, n = 257	Participants without Hyperglycemia at Admission, n = 388	*P*-Value
Procedure, n (%)							
Coronary angiography	379 (58.8)	132 (57.1)	247 (59.7)	.82	138 (53.7)	241 (62.1)	.08
Percutaneous coronary intervention	244 (37.8)	89 (38.5)	155 (37.4)	.78	91 (35.4)	153 (39.4)	.30
Bypass surgery	23 (3.6)	5 (2.2)	18 (4.3)	.15	5 (1.9)	18 (4.6)	.07
Medication during index admission, n (%)							
Aspirin	594 (92.1)	213 (92.2)	381 (92.0)	.93	234 (91.1)	360 (92.8)	.42
Ticlopidine or clopidogrel	546 (84.7)	195 (84.4)	351 (84.8)	.90	218 (84.8)	328 (84.5)	.92
Glycoprotein IIb and IIIa inhibitors	81 (12.6)	31 (13.4)	50 (12.1)	.62	28 (10.9)	53 (13.7)	.30
Unfractionated heparin	192 (29.8)	63 (27.3)	129 (31.2)	.30	70 (27.2)	122 (31.4)	.25
Enoxaparin	382 (59.2)	148 (64.1)	234 (56.5)	.06	154 (59.9)	228 (58.8)	.77
Medication at discharge, n (%)							
Aspirin	559 (86.7)	201 (87.0)	358 (86.5)	.84	210 (81.7)	349 (89.9)	<.01
Ticlopidine and clopidogrel	474 (73.5)	174 (75.3)	300 (72.5)	.43	187 (73.5)	287 (74.0)	.73
Beta-blockers	380 (58.9)	139 (60.2)	241 (58.2)	.63	150 (58.9)	230 (59.3)	.81
Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists	465 (72.1)	169 (73.2)	296 (71.5)	.65	195 (75.9)	270 (69.6)	.08
Statins	471 (73.0)	171 (74.0)	300 (72.5)	.67	189 (73.0)	282 (72.7)	.81
Insulin therapy	100 (15.5)	94 (40.7)	6 (1.4)	<.01	77 (30.0)	23 (5.9)	<.01
Length of stay, mean ± standard deviation	8.8 ± 7.2	9.6 ± 7.8	8.4 ± 6.8	.04	9.5 ± 7.4	8.4 ± 7.0	.06

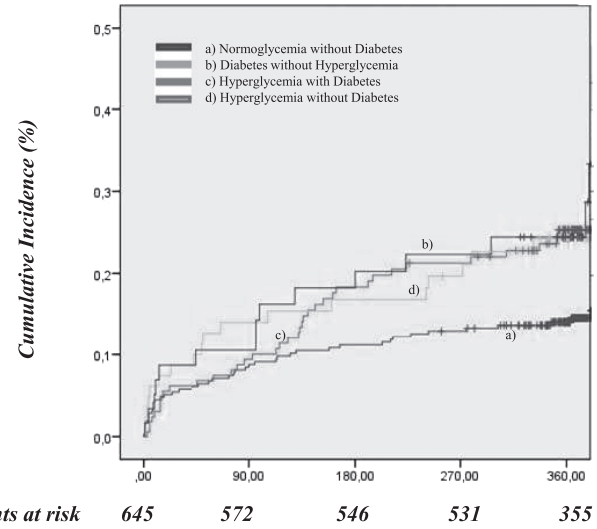

Figure 2. Cumulative incidence of mortality in the four mutually exclusive groups according to diabetic status and glucose category on admission.

sex were independent predictors of the composite endpoint at 1-year follow-up.

DISCUSSION

Approximately 30% of individuals with NSTEACS admitted to hospitals in Europe,[17,18] and in Italy,[19] are classified as having diabetes mellitus based on clinical history. In the general population with NSTEACS, which has a mean age of 67 in clinical trials and 70 to 73[20] in clinical practice, diabetes mellitus is a well-documented predictor of worse outcome. High blood glucose concentration, a common finding at admission in individuals across the spectrum of acute MI, has also been shown to be associated with greater mortality, especially in individuals without known diabetes mellitus.[4–9,21,22] Hyperglycemia on admission has been considered to be an acute stress response,[23] particularly in ST-segment elevation myocardial infarction (STEMI) with severe left ventricular dysfunction, but also as an index of previously undetected diabetes mellitus.[8] Whether the adverse prognostic effect of diabetic status and hyperglycemia on admission holds true in elderly adults with NSTEACS is uncertain because of the paucity of age-specific data. Because of this uncertainty, the 2012 consensus document of the American Diabetes Association on diabetes on older adults[24] has recommended specific research in hospitalized individuals.

The Italian Elderly ACS study has made the first attempt to investigate treatment strategies in individuals with NSTEACS aged 75 and older. Thirty-five percent of the participants had diabetes mellitus, and as expected, they had slightly worse baseline characteristics than participants without diabetes mellitus; they more frequently had a previous history of MI, heart failure, and stroke and had a lower average ejection fraction and hemoglobin levels, although mean glycated hemoglobin was only slightly higher, and renal function was similar to that of participants without diabetes mellitus, probably reflecting a "mild" diabetic status[24] or adequate care in participants with known diabetes mellitus. Data were not collected on the duration of diabetes mellitus, but the fact that only 34% of these participants were taking insulin seems to be consistent with the hypothesis of mild or well-compensated diabetes mellitus. Therefore, in this participant population, participants with diabetes mellitus had a clinical syndrome with prior cardiac involvement and residual damage but mild metabolic and renal impairment. One-year mortality was 47% higher than in participants without diabetes mellitus, but the contribution of diabetic status per se to the mortality model was nonsignificant, or at least it was obscured by other powerful markers of long-standing atherosclerosis, such as low ejection fraction and low eGFR.[16] One likely explanation might be that, in elderly adults with NSTEACS, diabetes mellitus has been among the causative factors of prior MIs and lower ejection fraction, which in turn become the most powerful predictors of mortality. The other side of the finding is that an octogenarian with NSTEACS and known diabetes mellitus but normal ejection fraction and renal function should not necessarily be considered at especially high risk of death at

Table 3. Predictors of 1-Year Mortality: Univariable and Multivariable Cox Regression Analysis

Predictor	Hazard Ratio (95% Confidence Interval)	*P*-Value
Univariable		
Age (1-year increase)[a]	1.092 (1.055–1.130)	<.001
eGFR (10-point increase)[a]	0.718 (0.645–0.800)	<.001
Hemoglobin level (1-point increase)[a]	0.794 (0.722–0.873)	<.001
Ejection fraction (1-point increase)[a]	0.947 (0.932–0.963)	<.001
High troponin	2.258 (1.334–3.822)	.002
Ischemic electrocardiographic changes	3.351 (1.753–6.404)	<.001
Diabetes mellitus	1.484 (1.035–2.126)	.03
Glycemia at admission (10-point increase)[a]	1.030 (1.008–1.052)	.008
Hyperglycemia at admission	1.565 (1.094–2.239)	.01
No diabetes mellitus and normoglycemic	1	
Hyperglycemia without known diabetes mellitus	1.887 (1.124–3.168)	.02
Diabetes mellitus without hyperglycemia	1.844 (1.028–3.308)	.04
Diabetes mellitus with hyperglycemia	1.709 (1.113–2.625)	.01
Multivariable with diabetes mellitus as covariate		
Ejection fraction (1-point increase)[a]	0.951 (0.935–0.969)	<.001
Hemoglobin levels (1-point increase)[a]	0.848 (0.765–0.940)	.002
Age (1-year increase)[a]	1.060 (1.018–1.104)	.004
eGFR (10-point increase)[a]	0.857 (0.751–0.976)	.02
Diabetes mellitus	1.258 (0.850–1.861)	.25
Multivariable with hyperglycemia as covariate		
Ejection fraction (1-point increase)[a]	0.952 (0.935–0.969)	<.001
Hemoglobin levels (1-point increase)[a]	0.840 (0.759–0.929)	.001
Age (1-year increase)[a]	1.056 (1.015–1.099)	.007
eGFR (10-point increase)[a]	0.858 (0.753–0.978)	.02
Hyperglycemia	1.180 (0.799–1.746)	.41

[a]Continuous variable.
eGFR = estimated glomerular filtration rate using the Cockroft-Gault formula.

1 year. As shown by the similar rates of angiography in individuals with and without diabetes mellitus, the study investigators did not consider diabetic status to be a trigger for taking or avoiding an invasive approach.

Several potential mechanisms have been hypothesized to explain the relationship between hyperglycemia at admission and prognosis in ACS, although a causal relationship could not be established. Hyperglycemia might be considered to be a marker of oxidative and inflammatory stress, although high glucose levels might have per se a causal role, particularly inducing myocardial injury.[8] The clinical and prognostic significance of hyperglycemia may be different in STEMI and non-STEMI (NSTEMI). In individuals with STEMI undergoing primary angioplasty, hyperglycemia has been shown to be a marker of extensive myocardial injury in the infarcted territory,[25] which is the hallmark of greater risk of major cardiovascular events at follow-up. In elderly adults with NSTEMI, the preexisting clinical burden, as described by left ventricular and renal dysfunction, seems to play a major role in terms of predicting acute hyperglycemia and subsequent mortality.

The incidence of hyperglycemia on admission depends on how hyperglycemic status is defined. The criterion for hospitalized individuals of 140 mg/dL (7.8 mmol/L) defined according to the 2013 American Diabetes Association Standard of Medical Care criteria,[12] was adopted based on previous large studies on the effect of glucose levels on mortality.[4–8] Using this cutoff, a larger proportion of hyperglycemic individuals was identified than in other studies,[9,21] although with fewer critical conditions. The retrospective analysis of the Cooperative Cardiovascular Project in a large population of individuals with MI (mostly STEMI) with a mean age of 76[9] established that the effect of baseline hyperglycemia on 1-year mortality was significant, and independent of covariates, only in individuals without known diabetes mellitus, whereas only severe levels of hyperglycemia affected individuals with diabetes mellitus. The Improving Cardiovascular Outcomes in Nova Scotia Investigators had similar findings,[21] whereas data from the Global Registry of Acute Coronary Events (GRACE) suggests that hyperglycemia on admission is associated with greater in-hospital mortality but not with mortality at 6-month follow-up.[22] No relationship between admission glucose and 1-year mortality, regardless of diabetic status, was observed in a large cohort of elderly adults (mean age 79) hospitalized for heart failure.[26]

Low eGFR and low ejection fraction were the only baseline variables significantly associated with hyperglycemia in the current study population, and this characteristic was associated with 1-year mortality in univariable analysis but was not an independent predictor of death in multivariable analysis. Maybe because of these worse baseline characteristics, individuals with hyperglycemia were less likely to undergo coronary angiography, although the rates of percutaneous coronary intervention and coronary artery bypass graft did not differ between glycemic groups.

Overall, although the study was not designed to support any hypothesis about glycemic control in ACS, the present data seem to suggest that intensive control of hyperglycemia after a NSTEACS may offer little benefit, at least in terms of mortality. Although two large interventional studies confirmed that glucose level at admission was a strong independent predictor of long-term mortality in participants with type 2 diabetes mellitus and ACS,[7,27] the same studies failed to prove that intensive glucose control in the acute phase provides any mortality benefit.[7,28] Interventional data in elderly adults are lacking, and because of this uncertainty, it is prudent to suggest moderate, rather than aggressive, glucose control in elderly adults with an ACS.[29]

The present study has limitations that may preclude making extensive inferences. First, like any trial comparing treatment strategies in NSTEACS, the Italian Elderly ACS trial excluded individuals with severe acute ischemia (deemed unsuitable for an initially conservative approach), so the conclusions about the modest prognostic role of hyperglycemia on admission may not apply to individuals with acute hemodynamic instability. Nevertheless, although the probability of acute hyperglycemia is higher in these individuals, this information is unlikely to be useful in decision-making. Second, the small sample size may have made the multivariable analysis underpowered, although the proximity of the hazard ratio to unity for diabetic status and hyperglycemia makes it unlikely that these variables have a clinically relevant effect in the general population of elderly adults with NSTEACS. Third, glucometrics other than admission glucose, such as fasting glucose[22] or average glycemia during the whole admission,[29] which may be more representative of the overall glycemic disturbance and has been shown to have prognostic relevance were not collected, although the results on hyperglycemia on admission are concordant with those of GRACE in showing no effect of admission glycemia on mortality,[22] whereas high fasting glycemia was predictive in that study.

In conclusion, there is a lack of data with regard to the prognostic effect of diabetes mellitus in elderly adults with NSTEACS. The results of the present study seem to show that diabetes mellitus in elderly adults with NSTEACS may have less of an effect on outcome than in younger people. Preexisting myocardial and renal damage, whether or not associated with diabetic status, are much more powerful predictors of mortality in this study population. In line with previous reports, the present study show that hyperglycemia on admission is associated with worse outcomes in elderly adults, although probably representing a marker of worse baseline characteristics rather than as causative factor.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. All-cause death and cardiovascular events (composite endpoint of all-cause death, myocardial infarction, stroke and rehospitalization for cardiovascular causes) occurring during index admission and within 1 year, subdivided by diabetic status (Figure S1A) and hyperglycemia upon admission (Figure S1B).

Table S1. Baseline characteristics of patients enrolled in the trial and in the registry stratified according to Diabetic status and Hyperglycemia (four mutually exclusive groups).

Table S2. Multivariable model including both "diabetes" and "hyperglycemia" as covariates.

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