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Impact of diabetes mellitus on outcomes in patients with acute myocardial infarction and systolic heart failure

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Aims To determine independent associations of diabetes mellitus with outcomes in a propensity-matched cohort of patients with acute myocardial infarction (AMI) and systolic heart failure (HF).

Methods and results In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial, hospitalized AMI patients complicated by left ventricular ejection fraction $\leq$40% and symptoms of HF receiving standard therapy were randomized 3–14 days post-AMI to receive eplerenone 25–50 mg/day ($n = 3319$) or placebo ($n = 3313$). Of the 6632 patients, 2142 (32%) had a history of diabetes, who were older and sicker. Using propensity scores for diabetes, we assembled a cohort of 1119 pairs of patients with and without diabetes who were balanced on 64 baseline characteristics. Incident fatal or nonfatal recurrent AMI occurred in 136 (12%) and 87 (8%) of matched patients with and without diabetes, respectively, during 2.5 years of follow-up [hazard ratio (HR) when diabetes was compared with no-diabetes, 1.61; 95% confidence interval (CI), 1.23–2.10; $P = 0.001$]. Diabetes was associated with nonfatal AMI (HR, 1.68; 95% CI, 1.23–2.31; $P = 0.001$) but not with fatal AMI (HR, 1.42; 95% CI, 0.88–2.28; $P = 0.146$). Hazard ratios (95% CIs) for the association of diabetes with all-cause mortality, cardiovascular mortality, all-cause hospitalization, and cardiovascular hospitalization were 1.12 (0.93–1.37; $P = 0.224$), 1.11 (0.90–1.37; $P = 0.318$), 1.13 (1.00–1.27; $P = 0.054$), and 1.20 (1.01–1.44; $P = 0.042$), respectively.

Conclusion In post-AMI patients with systolic HF, diabetes mellitus is a significant independent risk factor for recurrent short-term nonfatal AMI, but had no association with fatal AMI.

Keywords Diabetes • Recurrent myocardial infarction

Introduction

Diabetes mellitus is a risk factor for acute myocardial infarction (AMI).[1–3] Although the associations between diabetes and outcomes after AMI have been studied previously, the association of diabetes on recurrent AMI in a large cohort of post-AMI patients with systolic heart failure (HF) has not been well studied.[4,5] Further, associations between diabetes and poor outcomes have often been attributed to older age and higher prevalence of cardiovascular risk factors among those with diabetes. To what extent diabetes has an independent association with poor outcomes in post-AMI patients, however, is unclear. Traditional regression-based multivariable risk adjustment models may be limited by lack of procedural transparency, concerns for residual bias, and strong and often untenable model assumptions.[6] Propensity score matching, on the other hand, can be used to assemble cohorts in which patients are balanced on all measured baseline covariates and investigators are blinded to study outcomes.[7–13] Therefore, the objective of the current study was to examine the association of diabetes with outcomes in a propensity-matched cohort of post-AMI patients with systolic HF in which those with and without diabetes would be well-balanced on all measured baseline covariates.

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Methods

Source of study data

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) was a multicentre, international (37 countries), randomized, double-blind, placebo-controlled clinical trial that randomized 6632 patients with AMI complicated by symptoms of HF and left ventricular ejection fraction $\leq$40% between 27 December 1999, and 31 December 2001 to receive eplerenone 25–50 mg daily or placebo.[14] These patients were receiving standard medical therapy, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and coronary reperfusion therapies. The details of the design and results of the EPHESUS trial have been previously reported.[14] Patients with a serum creatinine $>$2.5 mg/dL or a potassium $>$5.0 mEq/L were excluded. An original copy of the EPHESUS data was obtained from Pfizer Inc., which was also the sponsor of the trial. However, Pfizer played no role in the design, analysis, and interpretation of the study data.

History of diabetes mellitus

Data on history of diabetes mellitus was collected by study investigators at baseline based on a physician diagnosis of diabetes. Although baseline data on random plasma glucose was collected, there was no data on baseline fasting plasma glucose. Of the 6632 EPHESUS participants, 2142 (32%) patients had a history of diabetes.

Study outcomes

For the current analysis, our main outcomes of interest were three AMI related endpoints: incident recurrent fatal or nonfatal AMI, mortality due to AMI, and hospitalization due to AMI during 2.5 years of follow-up (median, 16 months and range, 0.3–30.42 months). Incident AMI was confirmed using two of three usual criteria: (i) electrocardiographic changes including ST-segment elevation, new Q waves, or both for transmural AMI, and T-wave inversion, ST-segment depression, or both for subendocardial AMI, (ii) typical symptoms, or (iii) elevation of cardiac biochemical markers. Definite AMI (including silent AMI) was diagnosed by unequivocal electrocardiographic evidence of a new MI with or without a typical history, or a typical increase and decrease in biochemical markers of myocardial damage in which the maximal value reached was greater than twice the upper limit of the hospital range for creatine kinase, or in which the creatine kinase-MB fraction value was $\geq$10% of the creatine kinase value with either a typical history, new equivocal changes on electrocardiogram, or both, indicating the presence of ischaemia; or elevation of troponin to over three times the upper limit of the normal range of laboratory values. Acute myocardial infarction related to a cardiac procedure was diagnosed by a typical increase and decrease in biochemical markers of myocardial damage in which the maximal value reached within 1 week is more than three times the upper limit of the hospital range for creatine kinase after catheterization or percutaneous transluminal coronary angioplasty or greater than five times the upper limit of the hospital range for CK after cardiac surgery. A death was considered to be due to AMI if it occurred within 28 days after AMI, or when the occurrence of AMI and/or the date of occurrence of AMI were uncertain, the primary cause of death was confirmed by autopsy to be AMI.

Among the 2238 matched patients, a total of 223 (10%) patients had fatal or nonfatal incident AMI, 163 (7%) patients had hospitalization due to nonfatal AMI, and 70 (3%) patients had fatal AMI. None of the 163 patients died during hospitalization for AMI. However, of the 163 patients with nonfatal AMI, 40 (25%) patients subsequently died from all causes, of which 10 were due to recurrent AMI. We also examined other major natural history endpoints including mortality and hospitalization due to all causes and cardiovascular causes. The cause of death or the primary diagnosis leading to hospitalization was adjudicated by an EPHESUS critical-events committee, members of which were blinded to the patient's study drug assignment.

Assembly of a balanced cohort

Because of the imbalances in baseline covariates between patients with and without diabetes, we used propensity score matching to assemble a cohort, in which those with and without diabetes would be well-balanced on all measured baseline covariates.[7–13] The propensity score for diabetes for a patient is that patient's probability of having diabetes given his/her measured baseline characteristics. We estimated propensity scores for diabetes for each patient using a non-parsimonious multivariable logistic regression model. In the model, diabetes was the dependent variable and 64 clinically relevant baseline characteristics (*Figure 1*) were used as covariates.[7–11] Using a greedy matching protocol, we attempted to match each patient with diabetes with another patient without diabetes who had a similar propensity score. In five repeated steps, patients were matched by propensity scores to five, four, three, two, and one decimal places, the details of which have been described elsewhere.[7–11] In all, we were able to match 1119 pairs of patients with and without a history of diabetes with similar propensity for diabetes.

Because propensity score models are sample-specific adjusters and are not intended to be used for out-of-sample prediction or estimation of coefficients, measures of fitness and discrimination are not important for assessment of the model's effectiveness.[7–11,15,16] Instead, the reduction in baseline covariate imbalance is a better marker of the efficacy of a propensity score model, which is best assessed by estimating absolute standardized differences. Absolute standardized differences directly quantify the bias in the means (or proportions) of baseline covariates across the groups and are expressed as a percentage of the pooled standard deviations. Therefore, to quantify pre-match imbalances and post-match balances, we calculated pre- and post-match absolute standardized differences and presented those findings as Love plots.[8,11] An absolute standardized difference of 0% indicate no residual bias and $<$10% is considered of inconsequential bias.

Assembly of a pre-match cohort of similar sample size

To ensure that the post-match comparisions between patients with and without diabetes were not affected by the smaller sample size of the matched cohort, we assembled a pre-match cohort of the same sample size as that of the matched cohort. This was done by first identifying the 1119 patients with diabetes in the matched cohort. Then, we identified a random sample of 1119 patients without diabetes from the entire pre-match sample of 4490 patients without diabetes. Finally, we linked these two data sets, thus assembling a cohort of 1119 pairs of patients with and without diabetes.

Statistical analysis

For descriptive analyses, we used Pearson Chi-square and Wilcoxon rank-sum tests for the pre-match, and McNemar's test and paired sample *t*-test for the post-match comparisons of baseline covariates between patients with and without diabetes, as appropriate. We used Kaplan–Meier plots and matched Cox-regression analysis to estimate associations of a history of diabetes with outcomes during 2.5 years of follow-up. Log-minus-log scale survival plots were used to check proportional hazards assumptions. We then repeated our analysis in the pre-match cohort of 2238 patients. We performed subgroup analyses to determine whether the association between diabetes and

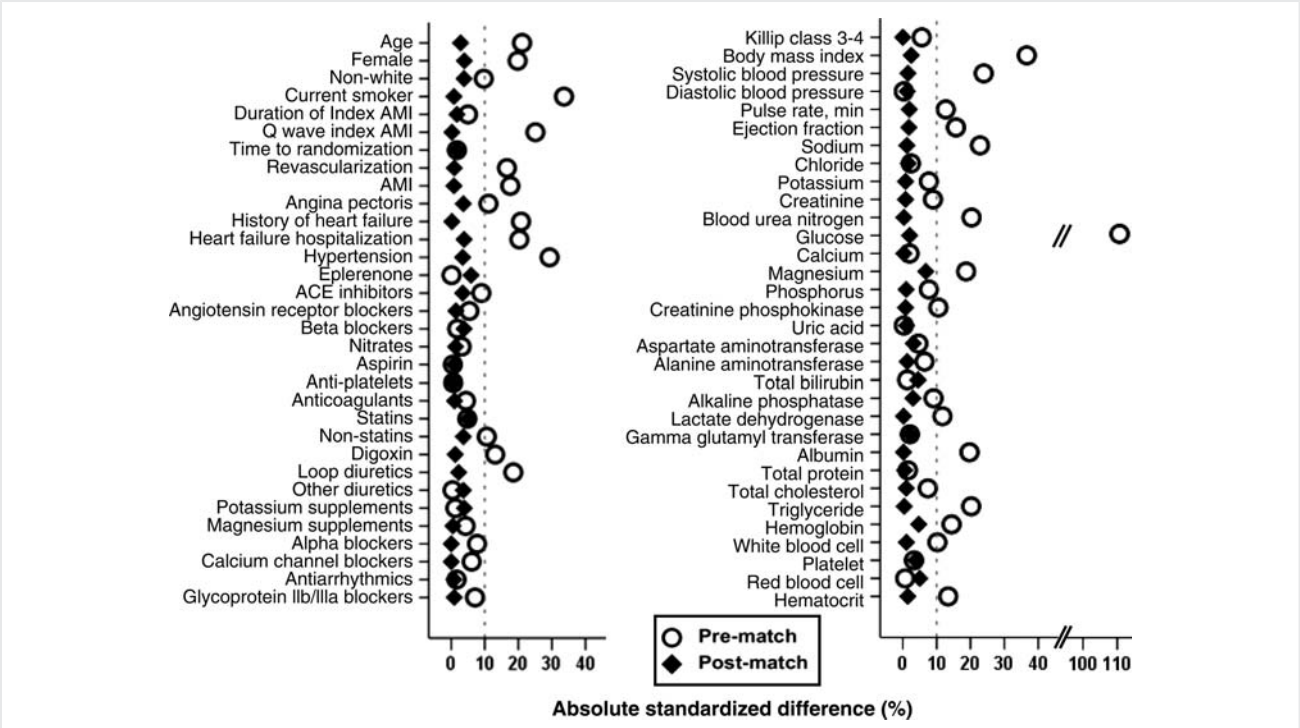

Figure 1 Love plots for absolute standardized differences for covariates between patients with and without a history of diabetes mellitus, before and after propensity score matching. AMI, acute myocardial infarction; ACE, angiotensin-converting enzyme.

recurrent fatal or nonfatal AMI was homogenous across various subgroups of matched patients. All statistical analyses were completed using SPSS for Windows, Rel. 15, 2006 (SPSS Inc., Chicago, IL, USA) and two-sided tests with a *P*-value < 0.05 were considered significant.

Sensitivity analysis

Despite excellent balance between matched patients with and without diabetes on all measured baseline covariates, confounding due to unmeasured covariates is still a possibility, as in all observational studies. A formal sensitivity analysis using Rosenbaum's formulation was conducted to quantify the degree a hidden bias that would need to be present to invalidate any conclusions based on significant associations between diabetes and primary outcomes among our matched patients.[17]

Results

Baseline characteristics

Matched patients had a mean age of 66 ($\pm$11) years, 31% were women and 10% were nonwhites. Before matching, patients with diabetes were older, had a higher prevalence of women, and a higher burden of cardiovascular comorbidities than those without diabetes. These and other imbalances in baseline characteristics between patients with and without diabetes were well-balanced after matching so that no significant differences remained (*Table 1*). Post-match absolute standardized differences for all measured covariates were $<$10% (most were $<$5%), suggesting substantial covariate balance across the groups (*Figure 1*).

Diabetes and recurrent fatal and nonfatal acute myocardial infarction

Fatal and nonfatal AMI occurred in 136 (12%) and 87 (8%) patients, respectively, with and without a history of diabetes [hazard ratio (HR) when diabetes was compared with no diabetes, 1.61; 95% confidence interval (CI), 1.23–2.10; $P = 0.001$; *Figure 2A* and *Table 2*]. In the absence of hidden bias, a sign-score test for matched data with censoring provides evidence ($P = 0.003$) that patients with a history of diabetes clearly had more incident fatal and nonfatal AMI than those without a history of diabetes. Our sensitivity analysis suggests that a hidden binary covariate, which is a near-perfect predictor of incident fatal and nonfatal AMI, would need to increase the odds of diabetes by 17% to potentially explain away this association. The results of our subgroup analyses demonstrated that a history of diabetes had, in general, a homogenous association with fatal and nonfatal AMI across a wide spectrum of patients (*Figure 3*).

Nonfatal AMI occurred in 101 (9%) and 62 (3%) patients, respectively, with and without a history of diabetes (HR, 1.68; 95% CI, 1.23–2.31; $P = 0.001$; *Figure 2B* and *Table 2*). A history of diabetes was not associated with fatal AMI (HR, 1.42; 95% CI, 0.88–2.28; $P = 0.146$; *Figure 2C* and *Table 2*). Among the 2238 random-pair patients, diabetes was significantly associated with fatal and nonfatal AMI (HR, 1.73; 95% CI, 1.31–2.27; $P < 0.001$), nonfatal AMI (HR, 1.73; 95% CI, 1.26–2.37; $P < 0.001$), and fatal AMI (HR, 2.00; 95% CI, 1.18–3.38; $P = 0.010$).

Table 1 Baseline patient characteristics by a history of diabetes mellitus before and after propensity matching

N (%) or mean (±SD)	Before propensity matching			After propensity matching		
	No history of diabetes mellitus (*n* = 1119)	History of diabetes mellitus (*n* = 1119)	*P*-value	No history of diabetes mellitus (*n* = 1119)	History of diabetes mellitus (*n* = 1119)	*P*-value
Age, years	63 (±12)	66 (±10)	<0.001	66 (±12)	66 (±10)	0.505
Women	300 (27)	339 (30)	0.068	359 (32)	339 (30)	0.375
Non-white race	110 (10)	110 (12)	1.000	123 (11)	110 (10)	0.413
Smoking status						
Current	405 (36)	270 (24)	<0.001	266 (24)	270 (24)	0.988
Never	411 (37)	495 (44)		502 (45)	495 (44)	
Former	303 (27)	354 (32)		351 (31)	354 (32)	
Duration of index AMI hospitalization, days	15.2 (±8.3)	15.3 (±8.7)	0.795	15.2 (±8.6)	15.3 (±8.7)	0.686
Index AMI with ST elevation	833 (74)	736 (66)	<0.001	735 (66)	736 (66)	1.00
Time from index AMI to randomization, days	7 (±3)	7 (±3)	0.774	7 (±3)	7 (±3)	0.697
Reperfusion or revascularization therapy within 14 days of index AMI						
CABG	11 (1)	10 (1)	0.826	11 (1)	10 (1)	1.00
PCI	257 (23)	256 (23)	0.960	255 (23)	256 (23)	1.00
Thrombolysis	332 (30)	258 (23)	<0.001	251 (22)	258 (23)	0.759
Past medical history						
AMI	280 (25)	338 (30)	0.006	342 (31)	338 (30)	0.890
Angina pectoris	433 (39)	497 (44)	0.006	517 (46)	497 (44)	0.415
Heart failure	140 (13)	211 (19)	<0.001	210 (19)	211 (19)	1.00
Heart failure hospitalization	71 (6)	107 (10)	0.005	120 (11)	107 (10)	0.393
Hypertension	635 (57)	746 (67)	<0.001	764 (68)	746 (67)	0.440
Medications						
Eplerenone	569 (51)	561 (50)	0.735	594 (53)	561 (50)	0.163
ACE-inhibitors	943 (84)	961 (86)	0.286	974 (87)	961 (86)	0.463
Angiotensin-receptor blocker	40 (4)	41 (4)	0.910	44 (4)	41 (4)	0.828
Beta-blockers	826 (74)	830 (74)	0.847	811 (73)	830 (74)	0.388
Nitrates	687 (61)	699 (63)	0.601	706 (63)	699 (63)	0.795
Aspirin	993 (89)	978 (87)	0.328	984 (88)	978 (87)	0.750
Anti-platelet drugs	314 (28)	312 (28)	0.925	309 (28)	312 (28)	0.926
Anticoagulants	187 (17)	177 (16)	0.567	173 (16)	177 (16)	0.861
Statins	506 (45)	535 (48)	0.219	507 (45)	535 (48)	0.240
Digoxin	160 (14)	204 (18)	0.012	199 (18)	204 (18)	0.824
Loop diuretics	592 (53)	672 (60)	0.001	684 (61)	672 (60)	0.628
Calcium channel blockers	167 (15)	189 (17)	0.204	189 (17)	189 (17)	1.00
Anti-arrhythmic drugs	135 (12)	147 (13)	0.445	150 (13)	147 (13)	0.900
Killip status						
I	105 (9)	218 (20)	<0.001	236 (21)	218 (20)	0.857
II	813 (73)	662 (59)		644 (58)	662 (59)	
III	163 (15)	200 (18)		196 (18)	200 (18)	
IV	38 (3)	39 (4)		43 (4)	39 (4)	
Body mass index, kg/m^2	26.9 (±4.2)	27.9 (±4.2)	<0.001	28.1 (±4.8)	27.9 (±4.2)	0.544
Systolic blood pressure, mmHg	118 (±16)	121 (±17)	<0.001	121 (±17)	121 (±17)	0.727
Diastolic blood pressure, mmHg	72 (±10)	72 (±11)	0.112	72 (±11)	72 (±11)	0.758
Pulse, bpm	74 (±11)	75 (±12)	0.053	75 (±12)	75 (±12)	0.653
Laboratory values						

Continued

Table 1 *Continued*

N (%) or mean (±SD)	Before propensity matching			After propensity matching		
	No history of diabetes mellitus (*n* = 1119)	History of diabetes mellitus (*n* = 1119)	*P*-value	No history of diabetes mellitus (*n* = 1119)	History of diabetes mellitus (*n* = 1119)	*P*-value
Sodium, mEq/L	140 (±4)	140 (±4)	0.059	139 (±4)	140 (±4)	0.765
Potassium, mEq/L	4.27 (±0.44)	4.25 (±0.45)	0.288	4.25 (±0.45)	4.25 (±0.45)	0.849
Creatinine, mg/dL	1.14 (±0.31)	1.16 (±0.35)	0.184	1.16 (±0.35)	1.16 (±0.35)	0.854
Glucose, mg/dL	111 (±33)	135 (±52)	<0.001	134 (±71)	135 (±52)	0.382
Albumin, g/dL	3.73 (±0.62)	3.67 (±0.57)	0.016	3.7 (±0.6)	3.7 (±0.6)	0.964
Haemoglobin, g/dL	13.3 (±1.7)	13.3 (±1.8)	0.505	13 (±2)	13 (±2)	0.277
Left ventricular ejection fraction, %	33.1 (± 5.9)	32.3 (± 6.2)	0.152	32.7 (±6.1)	32.8 (±6.2)	0.669

ACE, angiotensin converting enzyme; AMI, acute myocardial infarction, CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

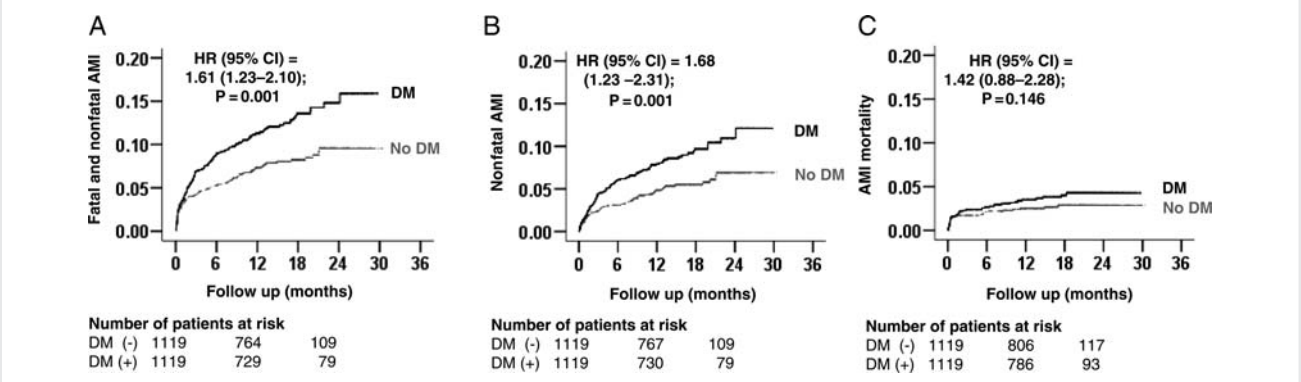

Figure 2 Kaplan–Meier plots for recurrent acute myocardial infarction (AMI) by a history of diabetes mellitus (DM): (*A*) fatal or nonfatal, (*B*) nonfatal, and (*C*) fatal. CI, confidence interval; HR, hazard ratio.

Diabetes and other outcomes

The presence of a history of diabetes had significant unadjusted associations with nearly all outcomes among the 2238 random-pair pre-match cohort (*Table 3*). However, among the 2238 balanced matched cohort, diabetes was only associated with increased risk of cardiovascular hospitalizations and held a borderline association with all-cause hospitalization. Pre- and post-match associations between diabetes and other outcomes are displayed in *Table 3*.

Diabetes and the effect of eplerenone

Among the pre-match 6632 EPHESUS participants, fatal or nonfatal AMI occurred in 293 (9%) and 313 (9%) patients in the eplerenone and placebo groups, respectively (HR when eplerenone was compared with placebo, 0.92; 95% CI, 0.79–1.08; $P = 0.312$; data not shown). As previously reported by the EPHESUS investigators, the effect of eplerenone on mortality did not vary by the presence or absence of diabetes at baseline.[14,18]

Discussion

Findings of the current analysis demonstrate that in post-AMI patients with systolic HF, a history of diabetes was associated with increased risk of recurrent fatal or nonfatal AMI, which was primarily driven by an increase in nonfatal AMI. Diabetes was also associated with cardiovascular hospitalization, but had no independent association with all-cause or cardiovascular mortality. To the best of our knowledge, this is the first report of an association between diabetes and recurrent AMI in a propensity-matched cohort of post-AMI patients with systolic HF. These findings provide important insights into the early effects of diabetes after AMI suggesting that nonfatal AMI may be the first major clinical cardiovascular manifestation after an index AMI in patients with diabetes. While there was no increase in fatal AMI or cardiovascular mortality in the diabetes group, it is likely that an excess of nonfatal AMI would over time result in progressive adverse left ventricular remodelling with ensuing worsening of left ventricular dysfunction leading to progressive chronic HF and associated morbidity and mortality.

Table 2 Association of a history of diabetes mellitus and recurrent acute myocardial infarction (AMI)

Outcomes	Events (%)		Absolute risk difference (%)	Hazard ratio (95% confidence interval)	*P*-value
	No history of diabetes	History of diabetes			
Before matching	($n = 1119$)	($n = 1119$)			
Fatal or nonfatal AMI	83 (7)	136 (12)	+5	1.73 (1.31–2.27)	<0.001
Nonfatal AMI	62 (6)	101 (9)	+3	1.73 (1.26–2.37)	0.001
Fatal AMI	21 (2)	41 (4)	+2	2.00 (1.18–3.38)	0.010
After matching	($n = 1119$)	($n = 1119$)			
Fatal or nonfatal AMI	87 (8)	136 (12)	+4	1.61 (1.23–2.10)	0.001
Nonfatal AMI	62 (6)	101 (9)	+3	1.68 (1.23–2.31)	0.001
Fatal AMI	29 (3)	41 (4)	+1	1.42 (0.88–2.28)	0.146

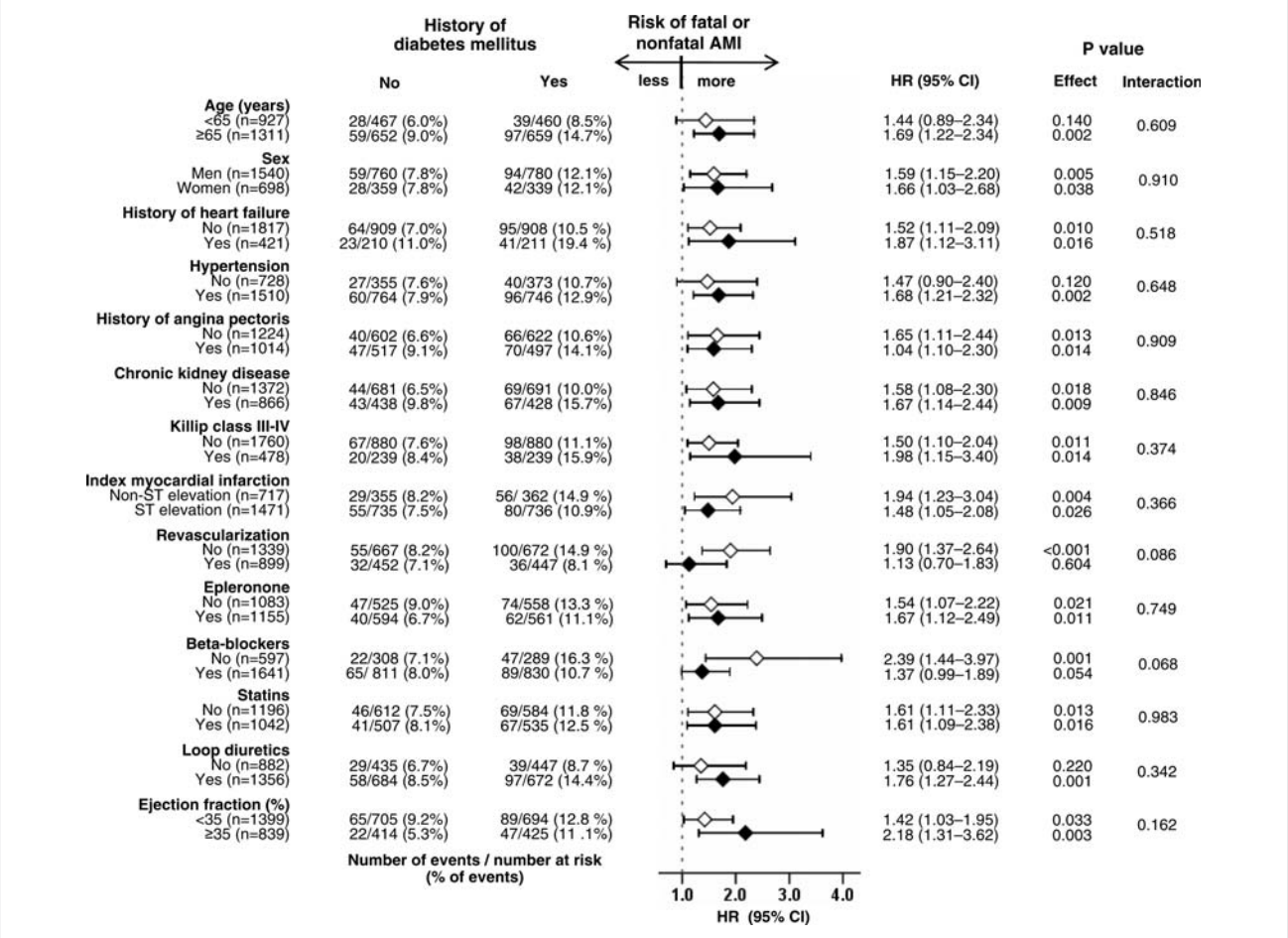

Figure 3 Association of a history of diabetes mellitus with subsequent fatal or nonfatal myocardial infarction in subgroups of patients. CI, confidence interval; HR, hazard ratio.

There are two potential explanations of the significant associations of diabetes with recurrent AMI in our balanced cohort of matched patients: residual confounding by measured covariates and cofounding due to unmeasured covariates. Because our matched patients were balanced on 64 baseline characteristics, they are unlikely to explain the observed associations. However,

Table 3 Effects of a history of diabetes on all other outcomes in EPHESUS

	Events (%)		Absolute risk difference (%)	Hazard ratio (95% confidence interval)	*P*-value
	No history of diabetes	History of diabetes			
Before matching	($n = 1119$)	($n = 1119$)			
All-cause death	148 (13)	212 (19)	+6	1.50 (1.21–1.85)	0.001
Cardiovascular death	129 (12)	182 (16)	+4	1.47 (1.17–1.84)	0.001
Heart failure death	34 (3)	50 (5)	+2	1.54 (1.00–2.38)	0.052
Sudden cardiac death	52 (5)	68 (6)	+1	1.37 (0.95–1.96)	0.089
All-cause hospitalization	494 (44)	554 (50)	+6	1.19 (1.06–1.35)	0.004
Cardiovascular hospitalization	190 (17)	263 (24)	+7	1.49 (1.23–1.79)	<0.001
Heart failure hospitalization	104 (9)	164 (15)	+6	1.67 (1.31–2.13)	<0.001
Cardiovascular hospitalization or cardiovascular death	283 (25)	374 (33)	+8	1.42 (1.21–1.65)	<0.001
All-cause hospitalization or all-cause death	578 (52)	650 (58)	+6	1.20 (1.07–1.34)	0.002
After matching	($n = 1119$)	($n = 1119$)			
All-cause death	191 (17)	212 (19)	+2	1.12 (0.93–1.37)	0.224
Cardiovascular death	166 (15)	182 (16)	+1	1.11 (0.90–1.37)	0.318
Heart failure death	47 (4)	50 (5)	+1	1.09 (0.73–1.62)	0.678
Sudden cardiac death	71 (6)	68 (6)	+0	0.97 (0.70–1.36)	0.867
All-cause hospitalization	506 (45)	554 (50)	+5	1.13 (1.00–1.27)	0.054
Cardiovascular hospitalization	225 (20)	263 (24)	+4	1.20 (1.01–1.44)	0.042
Heart failure hospitalization	150 (13)	164 (15)	+2	1.10 (0.89–1.38)	0.382
Cardiovascular hospitalization or cardiovascular death	349 (31)	374 (33)	+2	1.10 (0.95–1.27)	0.198
All-cause hospitalization or all-cause death	618 (55)	650 (58)	+3	1.08 (0.97–1.21)	0.169

it is possible that these characteristics may have changed during follow-up thus increasing the risk of subsequent AMI in those with diabetes.[19–22] Findings from our sensitivity analysis suggest that the association between diabetes and recurrent AMI was rather insensitive to an unmeasured binary confounder. The lack of an intrinsic association between diabetes and fatal AMI is likely due to a relatively small number of events and/or short follow-up of the EPHESUS trial. However, diabetes also had no intrinsic association with all-cause or cardiovascular mortality, despite much higher event rates for those outcomes, suggesting that the early effect of diabetes may not be fatal in nature.

The association between diabetes and recurrent nonfatal AMI may be a direct effect of diabetes. The metabolic effect of diabetes on cardiovascular morbidity and mortality is complex.[23–26] Diabetes is associated with activation of the renin–angiotensin–aldosterone system.[23,24] Collagen cross-linking is a major mechanism by which vascular and cardiac compliance is diminished in diabetes and may also contribute to diabetic cardiomyopathy.[25,26] Other potential underlying mechanisms may include accelerated atherosclerosis associated with diabetes. Hyperglycaemia, insulin resistance, and advanced glycation end-products have been implicated in vascular inflammation and endothelial dysfunction in patients with diabetes.[27] Further important contributing factors may include increased platelet activation, presence of a chronic hypercoagulable state, and impaired fibrinolysis.[28–30] Serum levels of insulin-like growth factor-binding protein-1 are elevated in patients with diabetes, which in turn has been shown to be associated with increased risk for cardiovascular mortality and morbidity in these patients.[19]

Studies of associations between a history of diabetes and outcomes after AMI are limited by relatively small sample size and failure to account for various important cardiovascular comorbidities and risk factors, including hyperglycaemia and hyperlipidaemia.[2–5,31–34] Further, only a few of these studies examined the association between diabetes and recurrent AMI.[4,5] In the Framingham Heart Study, of the 609 patients who survived an initial AMI, 92 had a history of diabetes and the age-adjusted incidence rates of recurrent AMI for participants with and without diabetes were approximately 650 and 400 per 10 000 person-years, respectively.[4] Findings from the Finnish Social Insurance Institution registry data suggest that of the 238 post-AMI patients, 169 had a history of diabetes and the unadjusted incidence rates of recurrent fatal and nonfatal AMI for participants with and without diabetes were 780 and 300 per 10 000 person-years, respectively.[5] In contrast to these studies, our study is distinguished by its contemporary nature, the presence of baseline systolic HF, larger sample size, the use of propensity-matched design to assemble a cohort that was balanced on 64 baseline covariates.

The findings of the current analysis are important as they help identify a subset of post-AMI patients who are at increased risk of subsequent nonfatal AMI. We observed that

diabetes-associated increased risk of recurrent AMI was higher in those not receiving beta-blockers and without coronary revascularization. The use of these therapies may explain the relatively low incidence of fatal AMI in our study. In the Framingham Heart Study, of the 609 patients who survived an initial AMI, 92 had a history of diabetes and the age-adjusted incidence rates of recurrent AMI for participants with and without diabetes were 724 and 326 per 10 000 person-years, respectively.[4] In contrast, the incidence rates for recurrent fatal AMI for matched patients with and without diabetes in our study were 291 and 200 per 10 000 person-years, respectively. Eplerenone has been shown to reduce adverse cardiovascular events in diabetes,[18] and may help improve long-term prognosis in these patients.

Our study has several limitations. We used a history of diabetes and the diagnosis of diabetes was not centrally adjudicated. Similarly, patients without diabetes at baseline may have developed diabetes during follow up, which may have led to regression dilution and underestimation of true association.[35] We also had no data on the duration, type, or control status of diabetes. The findings of the current study based on post-AMI patients with systolic HF may not be generalized to post-AMI patients without systolic HF.

In conclusion, in post-AMI patients with systolic HF receiving standard therapy, diabetes is a marker of poor outcomes. Although diabetes was independently associated with increased risk of recurrent nonfatal AMI during over 2 years of follow-up, there was no independent association with AMI mortality. Whether a more aggressive control of diabetes may reduce the risk of recurrent AMI in these patients is unknown and needs to be prospectively determined by future studies.

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