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Admission Glucose and Risk of Early Death in Non-Diabetic Patients with ST-Segment Elevation Myocardial Infarction: A Meta-Analysis

Authors' Contribution:
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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Impaired admission glucose (AG) is considered to significantly increase risk on both early and late death of the patients with ST-segment elevation myocardial infarction (STEMI), especially for non-diabetic patients; however, some reports contradict the relationship. We therefore conducted a meta-analysis to clarify this issue.





Material/Methods: PubMed, EMBASE, Web of Science, and Cochrane Library databases were systematically searched to identify all related prospective cohort studies. The relative risks (RR) with their 95% confidence interval (CI) were pooled quantitatively.

Results: The pooled RR of early outcome events indicated patients with glucose concentrations ≥ 6.1 –11.1 mmol/L had a 4.38-fold (95% CI, 3.23–5.94) higher early mortality. The pooled RR of late outcome events indicated that the patients with glucose concentrations ≥ 7.8 –11.1 mmol/L had a 1.65-fold (95% CI, 1.33–2.04) higher late mortality based on in-hospital or 30-day survivors.

Conclusions: High AG may be a helpful prognostic marker of significantly increased risk on early death in non-diabetic patients with STEMI, and has an explicit but prognostic adverse impact on long-term mortality but not early mortality in these patients.

MeSH Keywords: **Blood Glucose • Meta-Analysis • Myocardial Infarction**

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Background

Increased plasma glucose is a common feature in the acute phase of myocardial infarction, ranging from 3% to 71% in patients without diabetes [1,2]. Moreover, when serum markers of necrosis may still be normal, elevated plasma glucose levels can be detected within minutes of presentation, and then help to make appropriate decisions on treatment. It seems that the categorical variable elevated admission plasma glucose serves as a more powerful predictor than fasting glucose and the other elements of risk prediction markers such as elevated serum markers of myocardial infarction [3]. The patients with high admission glucose are more likely to develop restenosis and require repeat revascularization procedures than those with normal admission glucose. They also have increased risk for repeated myocardial infarction (MI) [4], stent thrombosis [5], and death [6], especially in non-diabetic patients [2], although some studies show inconsistent effects on the risk of late mortality [7–10]. Notably, most of these studies were conducted in the trials of fibrinolytic therapy as initial reperfusion strategy. Currently, limited evidence is available to propose admission glucose levels as an adverse prognostic factor in ST-segment elevation myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention (PCI) [11].

We therefore performed a meta-analysis of prospective studies published through August 2014 to evaluate the prognostic utility of admission glucose on early and late mortality in STEMI patients undergoing PCI without previous diagnosis of diabetes mellitus (DM).

Material and Methods

Selection of studies

Pertinent articles were searched in the electronic databases PubMed, EMBASE, Web of Science, the Cochrane Library from January 2000 to August 2014 using the terms “glycemic level” OR “glucose level” OR “blood glucose” OR “hyperglycemia” in conjunction with each of the following words: “percutaneous coronary intervention” OR “stent” OR “revascularization” OR “angioplasty” OR “PCI” OR “stenting” OR “reperfusion” OR “catheterization” OR “myocardial infarction”. In addition, conference proceedings/abstracts from major cardiology meetings were also searched in our analysis. For studies that did not report outcomes of interest, we contacted the authors for more information. The search was restricted to English- or Chinese-language articles.

Inclusion criteria

Only studies fulfilling the following criteria were included in the meta-analysis: (1) prospective clinical trials or cohort studies

in which all outcomes data had been collected prospectively; (2) the outcome was clearly defined as mortality after STEMI, including early (<30 days after admission) or late (>6 months after discharge) mortality; (3) admission glucose or hyperglycemia was quantified; (4) sufficient data on mortality or relative risks (RR) or odds risks (OR) and their 95% confidence interval (CI) were reported; (5) receiving PCI in adult non-diabetic patients with STEMI in each study group. In the case of a series of articles based on the same study, only the last published report was selected for analysis and the previous could be reviewed as supplementaries to missing data where applicable.

With a standardized manner, article search and review were performed independently by two investigators (Z-X.H and R.L). A third investigator (C-J.Z) was involved to adjudicate wherever discrepancies between the investigators occurred.

Data abstraction

The following data on pre-specified forms were abstracted: authors, year of publication, location of the study group, baseline features, death, myocardial infarction, characteristics of the study population (sample size, source of population and distribution of age, sex), follow-up duration, the RRs or ORs overall and in each subgroup and the corresponding CIs or standard errors, and the confounding factors matched or adjusted in the studies. The end-point of interest for the present analysis was the predictive value of admission glucose level for mortality in the first 30 days and late mortality in 30-day survivors. Two reviewers (Z-X.H and R.L) independently extracted the data in duplicate using a standardized protocol. Any disagreements were adjudicated by a third investigator (C-J.Z).

Study quality assessment

For assessment of trial quality, key indicators of study quality were extracted and methodological quality of each study was assessed by non-blinded independent reviewers according to the Newcastle-Ottawa Scale [12]. We assigned a categories of good (fulfilling 5 or more of the criteria), fair (meeting 4 of this criteria), and poor (fewer than 4 of this criteria) quality to all 4 criteria for quality standards. Discrepancies were also decided by discussion and consensus was made.

Statistical analyses

Relative risks for mortality were calculated separately for patients with high and low AG in each study. Unadjusted RRs were pooled using both fixed-effects or DerSimonian and Laird random-effects models, weighting by the inverse of the variance ($1/SE^2$) for each separate trial. Forest plots were generated to assess the RR estimates and corresponding 95% CIs across studies for graphical presentations. Statistical heterogeneity

was assessed by conducting Q tests. $P < 0.1$ was considered representative of significant statistical heterogeneity. I^2 values of more than 50% represent high heterogeneity, respectively. When effects were high heterogeneous, the randomized-effects model was used, otherwise, the fixed-effects model was used. In addition, the sources of heterogeneity were explored and meta-regression was performed. Variables included in the subgroup analyses were proportion of men, sample of participants, country of origin, and mean age of participants. We performed both the Egger test and Begg test to assess potential publication bias graphically using a funnel plot, in which log RR were plotted against their corresponding standard errors. Statistical analysis was performed by using Stata version 8.2 (Stata Corporation, College Station, TX, USA).

Results

Literature search

Totally, 1287 potentially relevant citations were found after an initial search. After excluding duplicates and screening the titles/abstracts, full publications of the remaining 119 articles were retrieved for further evaluation. Ultimately, of these 119 articles, 13 articles met the predetermined inclusion criteria and provided data adequate for meta-analysis (Figure 1).

Study characteristics

The 13 trials included in the meta-analysis were summarized in Table 1. Seven of the selected cohort studies [8,13–18] reported both the early and late outcome events, whereas 5 studies [19–23] only reported the early outcome events and one study [24] only report the late outcome event. Within the 13 trials, the mean age for non-diabetic participants ranged from 55 to 65 years, and the proportion of men in majority of the studies ranged from 68% to 88%, while 1 study reported mortalities stratified by sex [24].

Admission glucose and early mortality

At short-term follow-up, the point estimates of the unadjusted RR were consistently more than 1 in all studies, whereas 2 studies did not show statistically significant associations. As depicted in Figure 2, the pooled unadjusted relative risk of early mortality after STEMI in patients who had high AG was 4.38 (95% CI, 3.23–5.94) compared with patients with low AG. Statistical heterogeneity was significant for the analysis ($I^2 = 47.0\%$; P for heterogeneity 0.036) and stratified analyses showed that age and proportion of men were significantly related with the results (Table 2). Adjusted relative risks of early mortality after STEMI in patients with high AG were reported in 3 of the 12 studies [15,21,22], with a pooled relative risk

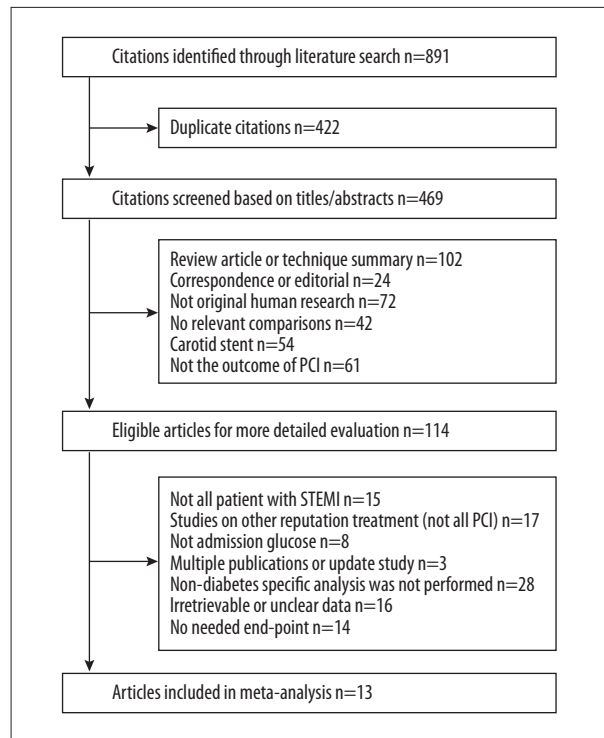


Figure 1. Study flow diagram of study selection process.

of 1.92 (95% CI, 1.63–2.26; Figure 2). One trial [18] showed that AG also had significant effect on early mortality (adjusted RR [per 1 mmol/L AG increased], 1.14; 95% CI, 1.09–1.19; Figure 2). Visual inspection of the funnel plot for the studies revealed symmetry. The funnel plot for the visual assessment of publication bias suggested no significant asymmetry (Figure 3A), and the Egger test ($P = 0.193$) and Begg test ($P = 0.193$) both indicated the absence of substantial publication bias.

Admission glucose and late mortality based on in-hospital or 30-day survivors

Seven trials showed that high AG was associated with a significantly higher risk of later mortality compared with lower AG group (pooled unadjusted RR, 1.65; 95% CI, 1.33–2.04; Figure 4). There was no statistically significant heterogeneity among the studies ($I^2 = 0.0\%$; P for heterogeneity 0.621). In the stratified analysis by follow-up time, ethnicity, mean age, proportion of men, cutoff level, and sample size, inconsistencies in these factors were not significantly related with the results. Moreover, 1 trial [14] reported the adjusted RR of late mortality after STEMI in patients who had high AG compared with patients with low AG on admission. In this trial, the RR of late mortality was significantly higher in the patients with high AG than that in the other patients (RR, 3.04; 95% CI, 1.06–8.73; Figure 4). One trial [18] showed that AG had no significant effect on later mortality (adjusted RR of per 1 mmol/L AG increased, 1.01; 95% CI, 0.93–1.11; Figure 4). As shown in Figure

Table 1. Characteristics of cohort studies evaluating prognostic utility of admission glucose on early and late mortality.

Author and Year	Participants	Mortality outcome		Direct stent (%)	Multiple vessel diseased (%)	Prior MI	Time to PCI (hour)	Final TIMI 3 (%)	Cutoff levels	Study quality
		Early	Late							
Ishihara et al. (2005) [8]	590 W and M (0.80) with mean age 63.2 years in Japan	30-day	3-year	75	35	12	4.7	88	11 mmol/L	Good
Kosuge et al. (2005) [21]	591 W and M (0.76) with mean age 65.9 years in Japan	Hospitalization	NR	80	10	10	3.51	90	11 mmol/L	Good
Vis et al. (2007) [17]	208 W and M(0.683) with mean age (NR) years in Netherlands	30-day	1-year	NR	49	20	NR	72	11.1 mmol/L	Good
Gasior et al. (2008) [16]	958 W and M (0.78) with mean age 57.0 years in Poland	Hospitalization	1-year	73	51	16	4.58	92	7.8 mmol/L	Good
Monte et al. (2008) [19]	126 W and M (NR) with mean age 63.7 years in Italy	30-day	NR	NR	NR	NR	NR	NR	6.1 mmol/L	Fair
Ergelen et al. (2010) [14]	1870 W and M(0.86) with mean age 55.7 years in Turkey	Hospitalization	More than 21 months	84	54	9.6	3.16	89	11.1 mmol/L	Good
Li et al. (2010) [20]	115 W and M (0.73) with mean age 65.8 years in china	Hospitalization	NR	NR	NR	NR	6.70	NR	7.8 mmol/L	Good
Timmer et al. (2011) [13]	4176 W and M(0.74) with mean age 62.2 years in Netherlands	30-day	1-year	87	49	8.9	NR	92	8.1 mmol/L	Good
Planer et al. (2012) [15]	2839 W and M(0.77) with mean age 59.5 years in USA and Europe	30-day	3-year	NR	NR	9.7	1.75	NR	8.1 mmol/L	Good
Hoebbers et al. (2012) [18]	1437 W and M(0.72) with mean age 61.0 years in Netherlands	30-day	3-year	83	33	12	3.06	91	7.8 mmol/L	Good
Otten et al. (2013) [24]	2872 M (1.0) with mean age 61.8 years in Netherlands	NR	1-year	NR	NR	10	NR	NR	NR	Good
Otten et al. (2013) [24]	115 W with mean age 66.5 years in Netherlands	NR	1-year	NR	NR	5.6	NR	NR	NR	Fair
Zhang et al. (2013) [22]	853 W and M (0.70) with mean age 62.1 years in china	Hospitalization	NR	90	53	NR	NR	84	10 mmol/L	Good
Ekmekci et al. (2013) [23]	503 W and M (0.88) with mean age 55.2 years in Turkey	Hospitalization	NR	NR	NR	NR	3.56	92	8.1 mmol/L	Good

CABG – coronary artery bypass graft; LVEF – left ventricular ejection fraction; M – men; NR – no report; PCI – percutaneous coronary intervention; RR – relative risk; TIMI – thrombolysis in myocardial infarction; W – women.

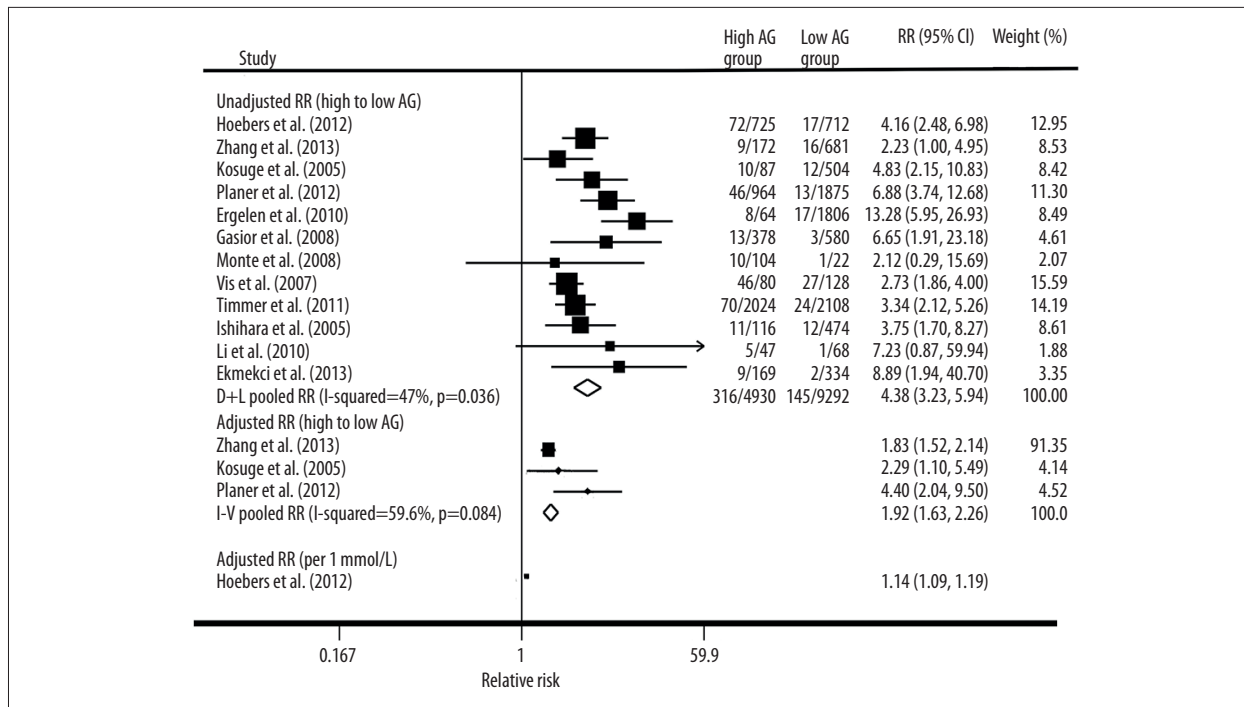


Figure 2. Forest plot of relative risk (RR) and 95% CI for high vs. low category of admission glucose and early death risk.

Table 2. Subgroups and metareg analysis of the association of admission glucose on early mortality.

Subgroups	Number of studies	Pooled RR (95% CI)	Heterogeneity		Meta-regression (P value**)
			P value*	I ²	
Follow-up time					
Hospitalization	6	5.890 (3.127, 11.095)	0.065	51.8%	0.226
30-day	6	3.708 (2.784, 4.938)	0.207	30.4%	
Ethnicity					
Yellows	4	3.540 (2.255, 5.558)	0.509	0.0%	0.467
Whites	8	4.834 (3.226, 7.244)	0.011	61.3%	
Mean age					
>60 years	8	3.278 (2.628, 4.088)	0.736	0.0%	0.003
≤60 years	4	8.482 (5.495, 13.092)	0.561	0.0%	
Men proportion					
>75%	6	6.566 (4.520, 9.537)	0.340	11.8%	0.008
≤75%	6	3.129 (2.462, 3.978)	0.652	0.0%	
Cutoff level					
>8.1mmol/L	5	4.157 (2.320, 7.451)	0.006	72.2%	0.626
≤8.1 mmol/L	7	4.453 (3.367, 5.889)	0.484	0.0%	
Sample size					
≤1000	8	3.254 (2.466, 4.294)	0.481	0.0%	0.224
>1000	4	5.583 (3.236, 9.631)	0.014	71.8%	

CI – confidence interval; RR – relative risk; * P<0.1 was considered significant; ** P<0.05 was considered significant.

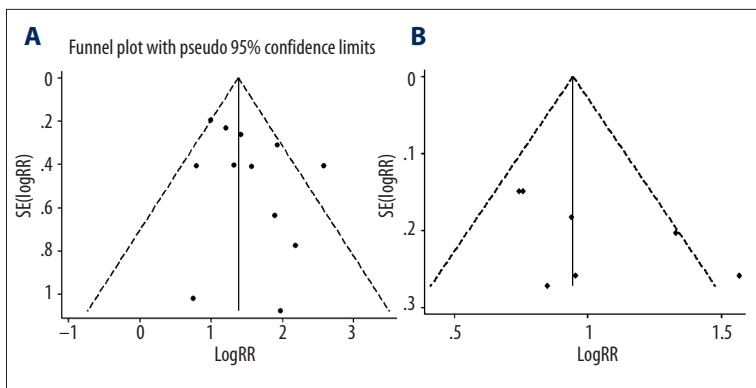


Figure 3. Funnel plots with 95% CI for (A) early death risk and late death risk based on in-hospital or 30-day survivors (B). RR, relative risk; SE, standard error.

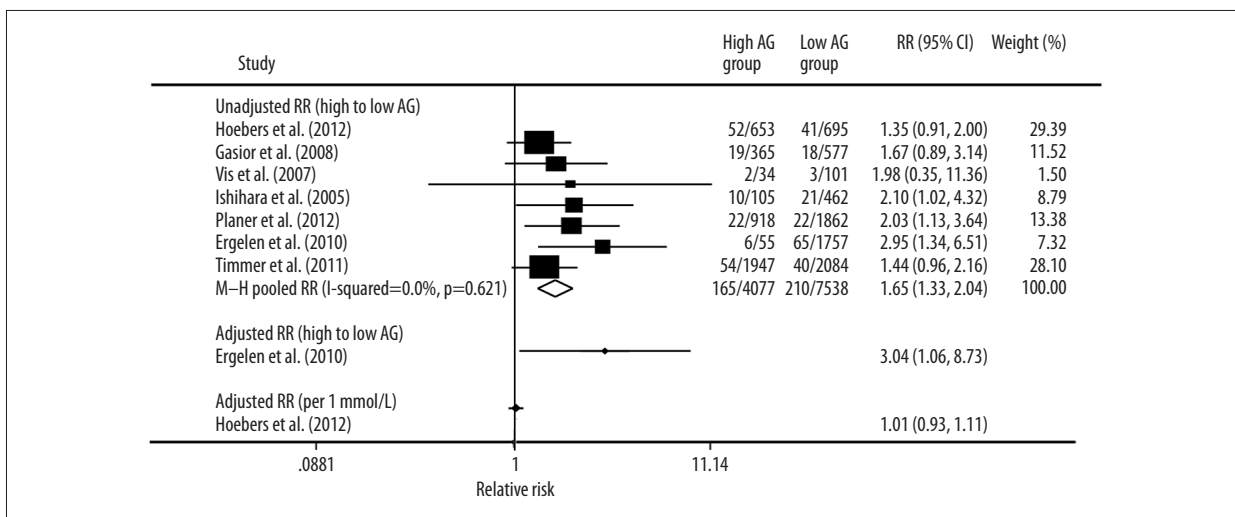


Figure 4. Forest plot of relative risk (RR) and 95% CI for high vs. low category of admission glucose and late death risk based on in-hospital or 30-day survivors.

3B, we did not find a significant publication bias for Egger’s test ($P=0.081$) and Begg’s test ($P=0.133$).

Discussion

The main finding from the 6 cohort studies indicated that the elevated AG was significantly associated with an increased risk of early death in the non-diabetes STEMI patients following PCI. Stratified analyses demonstrated that age and proportion of men may be the source of heterogeneity for early mortality but not late mortality based on in-hospital or 30-day survivors.

The mechanisms underlying the adverse effect of high AG in the STEMI patients with PCI are likely multifactorial, such as augmenting platelet-dependent thrombus formation [25], loss of the endothelial glycocalyx layer [26], inflammatory changes with adhesion molecule production [27], and direct glycation of coagulation factors to impair their function [28]. Recent animal studies have shown that increased myocardial uptake and metabolism of glucose during ischemia was associated

with preservation of myocardial function [30], and elevated free fatty acid levels reduced myocardial contractility and increased myocardial oxygen demand [31]. Hyperglycemia may precipitate an osmotic diuresis and deplete stroke volumes through interfering with the Frank-Starling mechanism [32]. Hyperglycemia also attenuated ischemic preconditioning by decreasing the activity of K-ATP channels [33].

The present meta-analysis showed that admission glucose was significantly associated with an increased risk of death for non-diabetic patients with STEMI following PCI. In term of the late mortality, the mortality based on in-hospital or 30-day survivors have their own strengths, with the former applied to evaluate the long-term risk of death before treatment and the latter applied to predict the long-term risk of death for patients still alive after 30 days of onset. Consistently, the meta-analysis also revealed a statistically significant increase of risk in patients who underwent PCI that was not consistently identified in the individual studies, whereas the prognostic effect was worse compared with early mortality. This indicates that the AG level was primarily an important marker of early risk,

reflecting, at least in part, the response to more severe stress due to larger infarctions and/or more severe hemodynamic compromise. On the other hand, the discrepancies between prognostic effect of early mortality and late mortality could result from the long-term benefits of early aggressive treatment.

These results suggest that physicians need to be aware that it is indispensable for the rapid delivery of appropriate treatment. At present, insulin-only and insulin-glucose with or without K infusions, which are used for strict control of glycemia following STEMI, seem to be the most acceptable management strategy [34]. The Hi-5 study demonstrated that early intensive treatment with insulin significantly decreased mortality in patients with AG > 144 mg/dL [35], although detrimental effects, such as excessive volume overload, hyperglycemia, and hypoglycemia, were clinically observed [36]. Strict glycemic control with insulin treatment after STEMI was downgraded from a class Ib to a class IIa recommendation in the recent update of the American Heart Association guidelines [18]. Recently, a new therapeutic approach, glucagon like peptide-1 (GLP-1) infusion [36], was proposed, which might improve cardiac function and reduce infarct size; it heralds a promising alternative approach for glycometabolic control in patients with STEMI.

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Conclusions

Taken together, the present meta-analysis revealed that impaired AG may be an effective prognostic marker of significantly increased risk on early death in non-diabetic patients with STEMI. To further confirm this conclusion, more high-quality and larger samplings of studies will be required in the future.

Conflict of interest statement

None declared.

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