Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/h8snm546

IMPACT OF RAISED GLUCOSE ON NON-DIABETIC PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION TREATED WITH PERCUTANEOUS CORONARY INTERVENTION

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Background
Increase glucose level is thought to significantly increase the risk of both early and late death with ST-segment elevation myocardial infarction (STEMI), especially for non-diabetic patients.
Increased plasma glucose is a common feature in the acute phase of myocardial infarction (MI), ranging from 3-71% in patients without diabetes. Moreover, when serum markers of necrosis may still be normal, plasma glucose levels are available within minutes of presentation and therefore facilitate appropriate treatment decision in a timely manner. It therefore seems likely that the categorical variable elevated admission plasma glucose would be a more powerful predictor than fasting glucose and the other elements of risk prediction markers such as elevated serum markers of myocardial infarction.In addition, patients with high admission glucose are more likely to develop restenosis and require repeat revascularization procedures compared with those with normal admission glucose, and are also at increased risk for repeated MI,stent thrombosis, and death,especially for non-diabetic patients although some studies showed inconsistent effects on the risk of late mortality. Conversely, the evidence linking admission glucose levels with an adverse prognosis in patients treated with primary percutaneous coronary intervention (PCI) is limited for patients with ST-segment elevation myocardial infarction (STEMI), even if PCI has been established to be significantly more effective than thrombolytic therapy. In view of the development of reperfusion therapy, it is uncertain if elevated admission glucose remains an independent determinant of early and late mortality in patients without previously diagnosed diabetes mellitus (DM).

MATERIALS AND METHODS
Pertinent articles were searched in the electronic databases PubMed, EMBASE, Web of Science, and the Cochrane Library through December 2013 using such terms as “glycemic level”, “glucose level”, “blood glucose”, and “hyperglycemia” in conjunction with each of the following words:

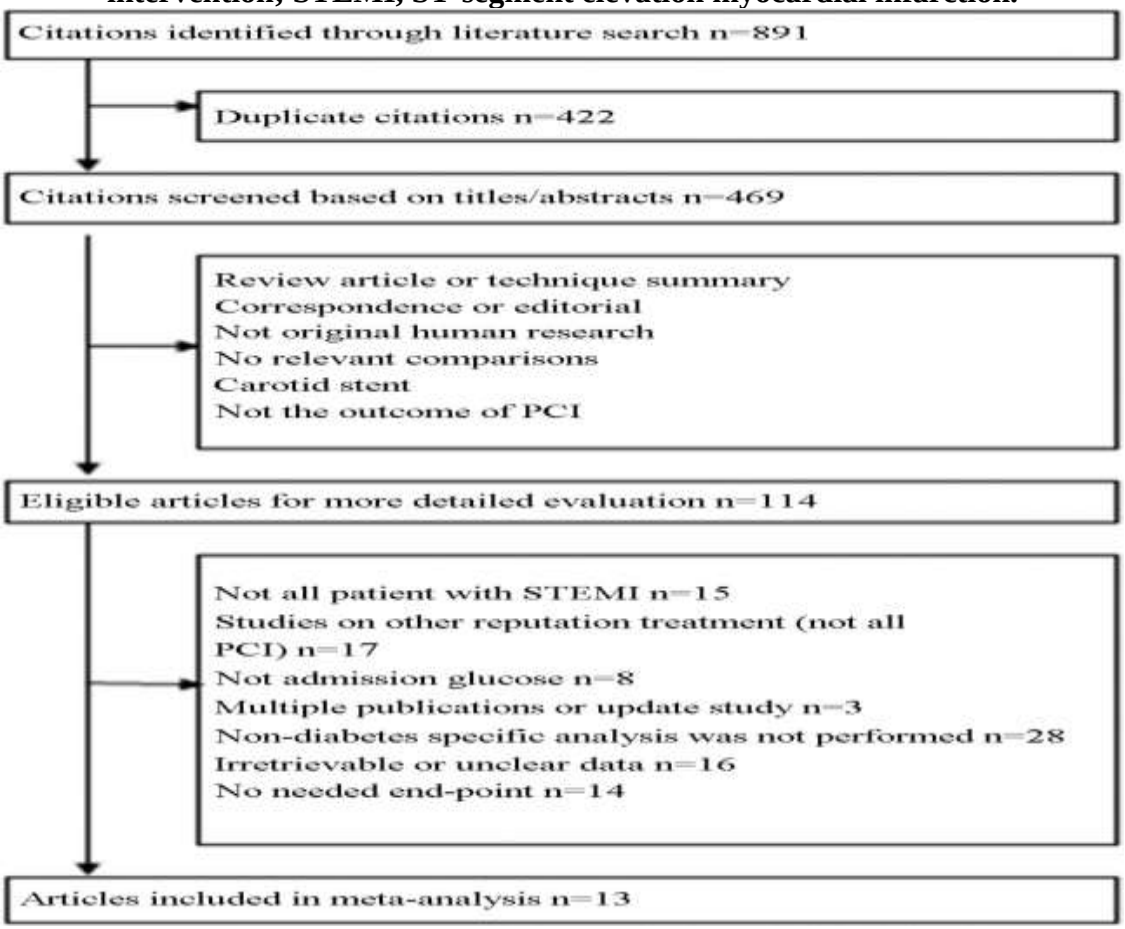
"percutaneous coronary intervention", "stent", "revascularization", "angioplasty", "PCI", "stenting", "reperfusion", "catheterization" or "myocardial infarction". In addition, conference proceedings/abstracts from major cardiology meetings were also searched and incorporated into our analysis. For studies that reported outcomes of interest we contacted the authors for more information. All studies retrieved were examined by first performing an initial screening of identified abstracts and titles by two independent reviewers, where disagreement was resolved after consensus. Studies that did not address the association between admission glucose or hyperglycemia and early or late mortality in patients with STEMI undergoing a PCI were excluded. The full texts of the remaining articles were then assessed as complete reports for the present meta-analysis according to the following explicit selection criteria: (1) prospective clinical trials or cohort studies in which all outcomes data had been collected prospectively; (2) the outcome was clearly defined as mortality, 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 (RRs) or odds risks and their confidence intervals (CIs) were reported; (5) receiving PCI in adult non-diabetic patients in each study group. Studies that did not report data on a no-diabetes subgroup were excluded.

RESULTS

Literature search

A total of 1287 potentially relevant citations were yielded after an initial database search as referenced herein. After excluding duplicates and screening the titles/abstracts, the complete publications of the remaining 119 articles were then retrieved for further evaluation.

Figure 1Study flow diagram of study selection process. PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.



Study characteristics

The 13 trials included in this meta-analysis are summarized in .Seven of the selected cohort studies,reported both the early and late outcome events, whereas 5 studies only reported the early outcome events and one study just reported the late outcome event. Within the 13 trials, the mean age for no-diabetic participants ranged from 55 years to 65 years and the proportion of men in majority of the studies ranged from 68-88%; one study reported mortalities stratified by gender .Relative risks of mortality after myocardial infarction, adjusted for age, sex, hypertension, current smoking, previous myocardial infarction, Killip class, in patients with high glucose were reported in 9 of the 13 studies.

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

Author and year	Participants	Mortality outcome	
		Early	Late
Ishihara et al. (2005)[15]	590 women and men (0.80) with mean age 63.2 years in Japan	30-day	3-year
Kosuge et al. (2005)[28]	591 women and men (0.76) with mean age 65.9 years in Japan	Hospitalization	NR
Vis et al. (2007)[24]	208 women and men (0.683) with mean age (NR) years in Netherlands	30-day	1-year
Gasior et al. (2008)[23]	958 women and men (0.78) with mean age 57.0 years in Poland	Hospitalization	1-year
Monte et al. (2008)[26]	126 women and men (NR) with mean age 63.7 years in Italy	30-day	NR
Ergelen et al. (2010)[21]	1870 women and men (0.86) with mean age 55.7 years in Turkey	Hospitalization	More than 21 months
Li et al. (2010)[27]	115 women and men (0.73) with mean age 65.8 years in china	Hospitalization	NR
Timmer et al. (2011)[20]	4176 women and men (0.74) with mean age 62.2	30-day	1-year

Author and year	Participants	Mortality outcome	
		Early	Late
	years in Netherlands		
Planer et al. (2012)[22]	2839 women and men (0.77) with mean age 59.5 years in USA and Europe	30-day	3-year
Hoebers et al. (2012)[25]	1437 women and men (0.72) with mean age 61.0 years in Netherlands	30-day	3-year
Otten et al.(2013)[31]	2872 men (1.0) with mean age 61.8 years in Netherlands	NR	1-year
Otten et al.(2013)[31]	115 women with mean age 66.5 years in Netherlands	NR	1-year
Zhang et al. (2013)[29]	853 women and men (0.70) with mean age 62.1 years in china	Hospitalization	NR
Ekmekci et al. (2013)[30]	503 women and men (0.88) with mean age 55.2 years in Turkey	Hospitalization	NR

Author and year	Direct stent (%)	Multiple vessel diseased (%)	Prior MI	Time to PCI (hour)	Final TIMI 3 (%)	Cutoff levels	Study quality
Ishihara et al. (2005)[15]	75	35	12	4.7	88	11 mmol/L	Good
Kosuge et al. (2005)[28]	80	10	10	3.51	90	11 mmol/L	Good
Vis et al. (2007)[24]	NR	49	20	NR	72	11.1 mmol/L	Good
Gasior et al. (2008)[23]	73	51	16	4.58	92	7.8 mmol/L	Good
Monte et al. (2008)[26]	NR	NR	NR	NR	NR	6.1 mmol/L	Fair

Author and year	Participants					Mortality outcome	
						Early	Late
Ergelen et al. (2010)[21]	84	54	9.6	3.16	89	11.1 mmol/L	Good
Li et al. (2010)[27]	NR	NR	NR	6.70	NR	7.8 mmol/L	Good
Timmer et al. (2011)[20]	87	49	8.9	NR	92	8.1 mmol/L	Good
Planer et al. (2012)[22]	NR	NR	9.7	1.75	NR	8.1 mmol/L	Good
Hoebers et al. (2012)[25]	83	33	12	3.06	91	7.8 mmol/L	Good
Otten et al.(2013)[31]	NR	NR	10	NR	NR	NR	Good
Otten et al.(2013)[31]	NR	NR	5.6	NR	NR	NR	Fair
Zhang et al. (2013)[29]	90	53	NR	NR	84	10 mmol/L	Good
Ekmekci et al. (2013)[30]	NR	NR	NR	3.56	92	8.1 mmol/L	Good

MI, myocardial infarction; NR, no report; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

Admission glucose and early mortality

Upon short-term follow-up, the point estimates of the unadjusted RR were consistently more than 1 in all studies, whereas two studies did not show statistically significant associations. As depicted in the pooled unadjusted relative risk of early mortality after STEMI in patients who had high AG on admission was 4.38 (95% CI, 3.23-5.94) compared with patients with low AG. Statistical heterogeneity was significant for these analyses (I^2 = 47.0%; p for heterogeneity 0.04), and stratified analyses showed age and proportion of men were significantly related to the results. Adjusted RRs of early mortality after STEMI in patients with high AG were reported in 3 of the 12 studies,with a pooled relative risk of 1.92 (95% CI, 1.63-2.26;). One trial showed that glucose also had significant effect on early mortality adjusted RR (per 1 mmol/L AG increased, 1.14; 95% CI, 1.09-1.19). 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 and the Egger's test (p = 0.19) and Begg's test (p = 0.19) both indicate the absence of substantial publication bias.

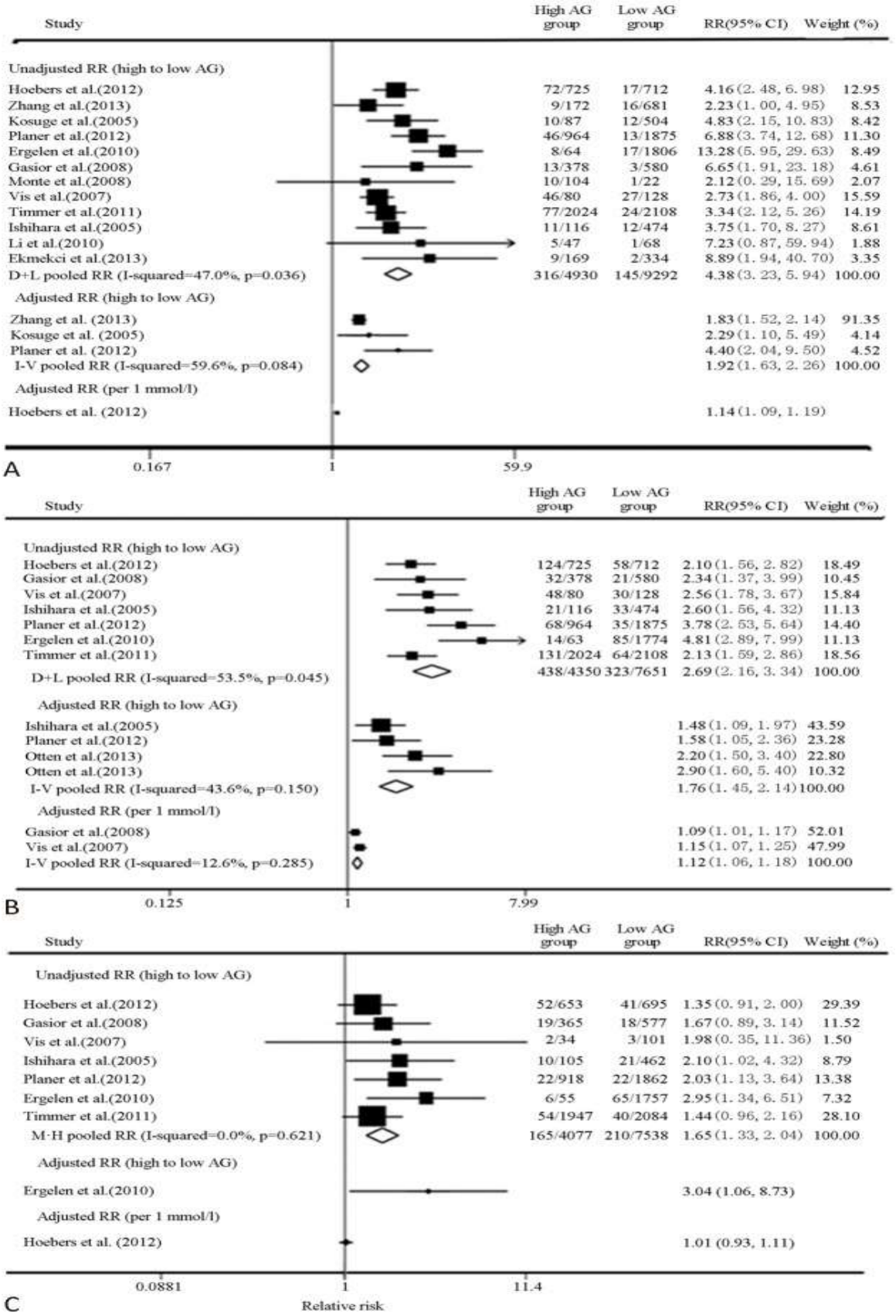


Figure 2: Relative risk (RR) of death by the follow-up duration. (A) Forest plot of RR and 95% confidence interval (CI) for high vs. low category of admission glucose and early death risk. (B) Forest plot of RR and 95% CI for high vs. low category of admission glucose and late death risk based on full participants. (C) Forest plot of RR and 95% CI for high vs. low category of admission glucose and late death risk based on in-hospital 30-day survivors.

Table 2: Subgroups and metareg analysis evaluating 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	5.89 (3.13, 11.10)	0.07	51.8%	0.23
30-day	6	3.71 (2.78, 4.94)	0.21	30.4%	
Ethnicity					
Yellows	4	3.54 (2.26, 5.56)	0.51	0.0%	0.47
Whites	8	4.83 (3.23, 7.24)	0.01	61.3%	
Mean age					
> 60 years	8	3.28 (2.63, 4.09)	0.74	0.0%	0.003
≤ 60 years	4	8.48 (5.50, 13.10)	0.56	0.0%	
Men proportion					
> 75%	6	6.57 (4.52, 9.54)	0.34	11.8%	0.008
≤ 75%	6	3.13 (2.46, 3.98)	0.65	0.0%	
Cutoff level					
> 8.1mmol/L	5	4.16 (2.32, 7.45)	0.006	72.2%	0.63
≤ 8.1 mmol/L	7	4.45 (3.37, 5.89)	0.48	0.0%	
Sample size					
≤ 1000	8	3.25 (2.47, 4.29)	0.48	0.0%	0.22
> 1000	4	5.58 (3.24, 9.63)	0.01	71.8%	

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CI, confidence interval; RR, relative risk; * $p < 0.1$ was considered significant; [#] $p < 0.05$ was considered significant.

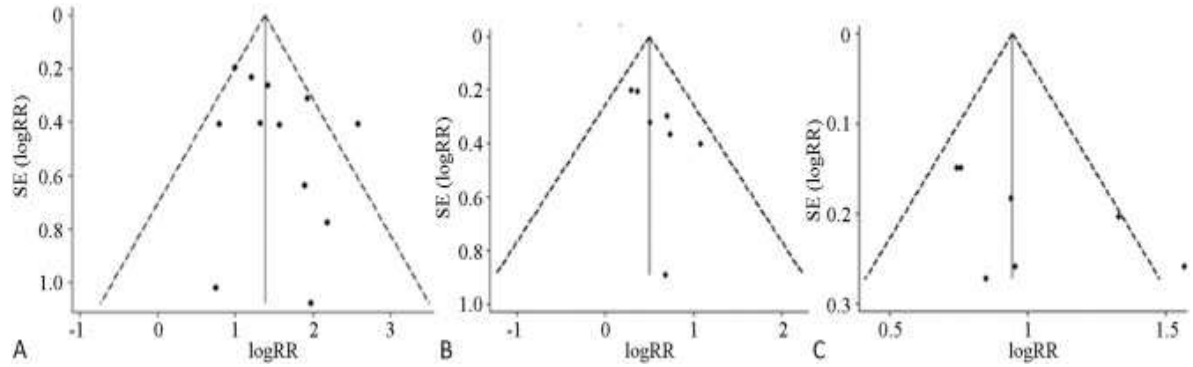

Figure 3: Funnel plots with 95% CI for (A) early death risk and late death risk based on full participants; (B) and in-hospital or 30-day survivors; (C) RR, relative risk; SE, standard error. CI, confidence interval.

Admission glucose and late mortality based on full participants

A summary plot showing the late mortality results of the comparison between the high and low categories of AG is shown in Figure 2B. Overall, compared with individuals with a low AG, those in

the high AG group had a significantly increased risk of developing late death, with a pooled RR of 2.69 (95% CI, 2.16, 3.34; Figure 2B). There was statistically significant heterogeneity among the studies (I^2 = 53.5%; p for heterogeneity 0.05). Stratified analyses did not show that age or proportion of men were significantly related with late mortality (Table 3). Similar outcomes were observed for adjusted RR (RR 1.76; 95% CI, 1.45 to 2.14; Figure 2B) and RR (per l mmol/L) (RR 1.12; 95% CI, 1.06 to 1.18; Figure 2B).[22,23] The symmetrical appearance of the funnel plots indicated a low potential publication bias, and neither the Egger's test (p = 0.14) nor the Begg's test (p = 0.37) suggested publication bias (Figure 3B).

Table 3: Subgroups and metareg analysis evaluating the association of admission glucose on late mortality

Subgroups	Number of studies	Late mortality based on full participants				Based on in-hospital or 30-day survivors			
		Pooled RR (95 % CI)	Heterogeneity		Meta-regression (p value#)	Pooled RR (95 % CI)	Heterogeneity		Meta-regression (p value#)
			p value*	I^2			p value*	I^2	
Follow-up time									
1-year	3	2.26 (1.83, 2.80)	0.73	0.0%	0.30	1.52 (1.09, 2.12)	0.89	0.0%	0.56
> 1 year	4	2.71 (2.22, 3.32)	0.02	71.3 %		1.68 (1.27, 2.23)	0.28	22.4 %	
Ethnicity									
Yellows	1	2.60 (1.57, 4.32)	NA	NA	0.92	2.10 (1.02, 4.32)	NA	NA	0.53
Whites	6	2.48 (2.13, 2.88)	0.02	61.9 %		1.58 (1.26, 1.97)	0.55	0.0%	
Mean age									
> 60 years	5	2.43 (2.07, 2.84)	0.16	38.9 %	0.32	1.55 (1.22, 1.96)	0.71	0.0%	0.35
≤ 60 years	2	2.96 (2.01, 4.38)	0.04	76.4 %		1.95 (1.18, 3.23)	0.26	21.9 %	
Men proportion									

Subgroups	Number of studies	Late mortality based on full participants				Based on in-hospital or 30-day survivors			
		Pooled RR (95 % CI)	Heterogeneity		Meta-regression (p value#)	Pooled RR (95 % CI)	Heterogeneity		Meta-regression (p value#)
			p value*	I^2			p value*	I^2	
> 75%	4	3.21 (2.51, 4.11)	0.17	40.8 %	0.06	2.01 (1.43, 2.82)	0.74	0.0%	0.15
≤ 75%	3	2.19 (1.82, 2.63)	0.66	0.0%		1.41 (1.07, 1.86)	0.90	0.0%	
Cutoff level									
> 8.1mmol/L	3	2.88 (2.22, 3.72)	0.11	55.4 %	0.38	2.34 (1.40, 3.91)	0.80	0.0%	0.17
≤ 8.1 mmol/L	4	2.38 (2.01, 2.83)	0.10	52.9 %		1.52 (1.20, 1.92)	0.70	0.0%	
Sample size									
≤ 1000	3	2.50 (1.92, 3.25)	0.95	0.0%	0.65	1.83 (1.16, 2.90)	0.89	0.0%	0.60
> 1000	4	2.48 (2.08, 2.95)	0.005	77.0 %		1.56 (1.22, 1.98)	0.27	23.4 %	

CI, confidence interval; NA, not available; RR, relative risk; * $p < 0.1$ was considered significant; # $p < 0.05$ was considered significant.

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 the lower AG group (pooled unadjusted RR, 1.65; 95% CI, 1.33-2.04;. There was no statistically significant heterogeneity among the studies ($I^2 = 0.0\%$; p for heterogeneity 0.62). 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 to the results . Moreover, one trial reported the adjusted RR of late mortality after STEMI in patients who had elevated AG on admission 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 in the other patients (RR, 3.04; 95% CI, 1.06-8.73;). One trial 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;. As shown in , we did not find a significant publication bias for Egger's test ($p = 0.08$) and Begg's test ($p = 0.13$).

DISCUSSION

The principal finding from the six cohort studies involved data on evaluating the effects of admission glucose on prognosis of non-diabetes patients with STEMI indicated that it was significantly associated with an increase in the risk of early death following PCI. Regarding long-term outcomes based on full population or early survival, high admission glucose has also an explicit but poorer prognostic impact on long-term mortality than early mortality. Stratified analyses demonstrated that age and proportion of men may be the source of heterogeneity for early mortality rather than late mortality. This suggests that men and older people have a worse prognosis, while there is no significant difference between the different ages or sexes if they survive in the early stages of the disease, which is consistent with our experience in a clinical environment.

Patient stress response, accompanied by high levels of catecholamines,[30,31] such as cortisol and adrenaline, may be responsible for the elevated admission glucose concentration.[2,32] These hormones promote glycogenolysis and lipolysis, resulting in elevated glucose and free fatty acid levels. This antagonizes insulin, a result which is frequently observed in non-diabetic patients with STEMI. Besides, hyperglycemia may be a reflection of pre-existing impaired glucose tolerance or undiagnosed DM.[33] Some studies have showed that approximately two-thirds of patients without previous diagnosis of diabetes have impaired glucose tolerance or undetected diabetes.[34-36]

The potential biological mechanism of adverse effect on the diminished benefit of PCI in patients with high admission glucose likely is multifactorial, such as augmenting platelet-dependent thrombus formation,[37] loss of the endothelial glycocalyx layer,[38] which harbors coagulation factors, inflammatory changes with adhesion molecule production[39,40] and direct glycation of coagulation factors, affecting their function.[26,41] Furthermore, excess free fatty acid levels, accompanied by relative insulin deficiency, are toxic to ischemic myocardium.[42] Animal studies have recently shown that increased myocardial uptake and metabolism of glucose during ischemia was associated with preservation of myocardial function,[43] whereas increased free fatty acid levels reduced myocardial contractility and increased myocardial oxygen demand.[44] Another potential mechanism is that hyperglycaemia may precipitate an osmotic diuresis and deplete stroke volumes through interfering with the Frank-Starling mechanism. Hyperglycemia also attenuates ischemic preconditioning by decreasing the activity of K-ATP channels.[45]

Consistent with the results of the present analysis, this meta-analysis showed that admission glucose was significantly associated with an increase in the risk of death for non-diabetic patients with STEMI following PCI. The previous study showed that the risk of early death was significantly increased for patients with high admission or fasting glucose, followed by low rates of intensive reperfusion therapy. In our study, we extended these results to demonstrate that this is consistent, for patients uniformly treated with PCI, with the previous report.

In terms of late mortality, the mortality based on full participants and in-hospital or 30-day survivors have their own strengths, with the former applicable to evaluate the long-term risk of death before treatment and the latter applicable to predict the long-term risk of death for patients still alive 30 days after onset. Similar to the early mortality, our meta-analysis also revealed a statistically significant increased risk in patients who underwent PCI that was not consistently identified in the individual studies, whereas the prognostic effect was poorer compared with early mortality. This would indicate that admission glucose level is primarily an important marker of early risk, reflecting, at least in part, the response to a more severe stress due to larger infarctions and/or more severe hemodynamic compromise. On the other hand, an alternative explanation for the discrepancies between prognostic effect of early mortality and late mortality could be due to the long-term benefits of early aggressive treatment.

These results suggested that physicians need to be aware that it was indispensable for the rapid delivery of appropriate treatment. At present, insulin only and insulin-glucose with or without K infusions, used for strict control of glycemia following STEMI, appear to be the acceptable management strategy.[46] The Hi-5 study demonstrated that early intensive treatment with insulin significantly decreased mortality in patients with admission glucose concentrations above 144

mg/dL,[47] whereas, detrimental effects have been observed in clinical practice[48] such as excessive volume overload, hyperglycemia, and hypoglycemia. Strict glycemic control with insulin treatment after STEMI, as a consequence, was downgraded from a class Ib to a class IIa recommendation in the recent update of the American Heart Association guidelines.[13] Recently, a new therapeutic approach was proposed, glucagon-like peptide-1 (GLP-1) infusion,[48] which exerts insulinotropic and insulinomimetic actions. According to experimental studies, it might improve cardiac function and reduce infarct size, heralding a promising alternative approach for glycometabolic control in patients with STEMI.

Our meta-analysis has several strengths. First, most of the articles included in the study had an extended duration of follow-up and a large sample size. Second, we report both the unadjusted and adjusted effect size, making the results more comprehensive and credible. Moreover, compared with the previous meta-analysis, the study minimized clinical heterogeneity because of the same exposure factor (i.e., admission glucose), the same disease (i.e., STEMI), and the same treatment (i.e., PCI). Additionally, the consistent association among subgroups, stratified by characteristics of participants, indicates that the conclusions were not dependent on arbitrary decisions in the meta-analysis.

This study did have several limitations that merit consideration when interpreting the results. which include study selection bias, between-study heterogeneity and inability to adjust for baseline differences because individual level data were not available. In the meta-analysis, the Egger's regression test and visual inspection of a funnel plot for publication bias did not show a substantially bias. Nevertheless, it is still very likely that studies with negative results are underpublished, even though the tests for publication bias are not significant. Moreover, the present study was based on observational studies. Hence, patients in observational studies are subject to a large treatment bias and other confounding effects because of the lack of random allocation. These biases influence the evidence-based strength of this study. More high quality, larger samplings of studies will be required in the future.

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