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Original Article

Admission hyperglycemia is associated with reperfusion failure in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: a systematic review and meta-analysis

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Abstract: Background: Admission hyperglycemia (AH) is a common finding in patients with acute coronary syndrome and has been reported to be associated with increased morbidity and mortality. Prior studies suggest that AH could be associated with reperfusion failure. We conducted a systematic review and meta-analysis to explore an association between AH and risk of reperfusion failure in patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI). Methods: Two investigators searched the databases of MEDLINE and EMBASE from inception to February 2021. Study eligibility was independently determined by two investigators and needed to demonstrate association of AH and rate of reperfusion failure, or sufficient raw data to calculate the effect size. Participants were classified into two groups corresponding to their level of admission hyperglycemia. Group 1 was defined as an AH of ≥120-150 mg/dl, and group 2 as ≥150-200 mg/dl. Data from each study were combined using the random-effects model, the generic inverse-variance method of Der Simonian and Laird. The heterogeneity of effect size was quantified using the I^2 statistic. A sensitivity analysis was performed by omitting one study at a time. Publication bias was assessed using a funnel plot and the Egger's test. All data analyses were performed using STATA SE version 14.2. Results: A total of ten studies from 2008 to 2019 met eligibility criteria and were included in the final analysis. We found that AH is associated with increased risk of reperfusion failure in both group 1 (pooled OR=1.78, 95% CI: 1.35-2.33, I^2=63.2%, P<0.001) and group 2 (pooled OR=1.44, 95% CI: 1.14-1.82, I^2=57.1%, P<0.001). Sensitivity analysis showed that none of the results were significantly altered after removing one study at a time. In subgroup analysis of non-diabetic patients, we found that AH is also associated with increased risk of reperfusion failure in both group 1 (pooled OR=1.81, 95% CI: 1.29-2.54, P<0.001) and group 2 (pooled OR=1.61, 95% CI: 1.17-2.21, P<0.001). We did not perform a funnel plot or Egger's test as the number of available outcomes was insufficient to reject the assumption of funnel plot asymmetry. Conclusions: Our systematic review and meta-analysis demonstrated that AH is associated with increased risk of reperfusion failure in STEMI patients undergoing pPCI, in the non-diabetic population.

Keywords: ST-elevation myocardial infarction, hyperglycemia, reperfusion failure, coronary reperfusion

Introduction

Hyperglycemia is a common finding in patients admitted to the hospital and associated with higher in-hospital mortality rate and poor clinical outcome in patients with and without diabetes mellitus (DM) [1]. Stress hyperglycemia is defined by the American Diabetes Association (ADA) as having a random glucose level greater than 140 mg/dl at any given time in hospitalized patients [2]. Admission hyperglycemia (AH) is further defines as similarly having a glucose level greater than 140 mg/dl upon presentation to the hospital. Up to 58% of patients with acute coronary syndrome (ACS) experience AH [3]. More than half of patients with ACS e hyper-

glycemia were not documented to have underlying diabetes. Admission hyperglycemia has been reported to be associated with increased morbidity and in-hospital mortality in patients with acute myocardial infarction and overall worse cardiovascular outcomes [4-9]. More specifically, evidence showed that patients with AH have larger infarct size and more myocardial necrosis, higher risk to develop cardiomyopathy and heart failure with worse ventricular function, and ultimately higher overall mortality rate [4-9]. These outcomes were found consistently in both diabetic and non-diabetic populations [5-12]. However, the underlying mechanisms of these associations are currently unknown.

Prompt reperfusion therapy with primary percutaneous coronary intervention (pPCI) is essential to optimize myocardial salvage and to reduce mortality of ST-elevation myocardial infarction (STEMI) [13, 14]. However, 25% to 30% of patients with ACS may lack of microvascular reperfusion despite successful coronary recanalization of the epicardial vessels as shown by angiography [15]. Some studies suggest that AH could be associated with failure of reperfusion therapy [16-18]; which could lead to worse cardiac remodeling as mentioned above. However, there are conflicting outcomes between published studies. Current guidelines for STEMI patients focus on glucose management following the pPCI but did not mention proper glucose control pre-operation [19, 20]. This analysis of the possible effects of AH on reperfusion failure in the STEMI population could be used as a framework to further develop protocols to manage AH pre-procedure to improve clinical outcomes. Hence, we conducted this systematic review and meta-analysis to explore a relationship between AH and risk of reperfusion failure in patients with STEMI undergoing pPCI.

Methods

Search strategy

Two investigators (MA and AT) independently searched for published studies indexed in the MEDLINE and EMBASE databases from inception to February 2021 using a search strategy including the terms “hyperglycemia”, “percutaneous coronary intervention”, “coronary reperfusion”, as described in Supplementary File 1. Only full articles in English and studies conducted in cohorts were included. A manual search for additional pertinent studies using references from retrieved articles was also completed.

Inclusion criteria

The eligibility criteria included the following: (1) Cohort studies (prospective or retrospective), case-control studies, cross-sectional studies, and randomized control trials conducted in STEMI patients undergoing pPCI. Studies need to report incidence of AH and rate of reperfusion failure. (2) Relative risk (RR), odds ratio (OR), hazard ratio (HR) with 95% confidence interval (CI), or sufficient raw data to perform the above calculations were provided. Patients without AH were used as controls.

Study eligibility was independently determined by two investigators (MA and AT) and differences were resolved by mutual consensus.

Data extraction and quality assessment

A standardized data collection form was used to obtain the following information from each study: name of first author, study design, country of study, year of publication, total participants, study population, demographic data and definition of AH.

Two investigators (MA and AT) independently performed this data extraction process to ensure accurate data extraction. Any data discrepancy was resolved by reviewing the primary data from the original articles.

The Newcastle-Ottawa quality assessment scale (NOS) was used to assess each study’s quality. The Newcastle-Ottawa scale uses a star system (0 to 9) to evaluate included studies on 3 domains: in three domains: recruitment and selection of the participants, similarity and comparability between the groups, and ascertainment of the outcome of interest among cohort and case-control studies. Higher scores represent higher study quality [21]. The Cochrane collaboration tool for assessing risk of bias was used to evaluate the quality of each randomized controlled trial by assessing as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other) [22].

Definition

ST-elevation myocardial infarction: It was defined by at least two contiguous leads with ST-segment elevation ≥2.5 mm in men <40 years, ≥2 mm in men ≥40 years, or ≥1.5 mm in women in leads V2-V3 and/or ≥1 mm in the other leads [23].

Reperfusion failure: It was defined by Thrombolysis In Myocardial Infarction (TIMI) flow grade following pPCI or of 0, 1 or 2 of the infarct-related artery.

Admission hyperglycemia: It was defined as venous blood glucose or capillary blood glucose measured on admission greater than 140 mg/dl [2]. Each study defined AH differently as shown in **Table 1**.

Statistical analysis

We performed a meta-analysis of the included studies using a random-effects model. Studies were excluded if they did not report an outcome in each group or did not have enough information available to calculate the OR or RR. We pooled the point estimates of RR and OR from each study using the generic inverse-variance method of Der Simonian and Laird [24]. The heterogeneity of effect size estimates across these studies was quantified using the I^2 statistic. The I^2 statistic ranges in value from 0 to 100% (I^2<25%, low heterogeneity; I^2=25%-0%, moderate heterogeneity; and I^2≥ 50%, substantial heterogeneity) [25]. A sensitivity analysis was performed to assess the influence of the individual studies on the overall results by omitting one study at a time. Publication bias was assessed using a funnel plot and the Egger's regression test [26]; (P<0.05 was considered significant). All data analyses were performed using STATA SE version 14.2.

Results

Search results

Our search by the search strategy from section 2.1 yielded 856 potentially relevant articles (396 articles from EMBASE and 460 articles from MEDLINE). After the exclusion of 393 duplicated articles, 463 articles underwent title and abstract review. At this stage, 435 articles were excluded at this stage since they were not cohort/case-control studies, cross-sectional studies or randomized controlled trials, were review articles, were not conducted in population of interests, or topics were not relevant. This left 28 articles for full-length review. Further 18 articles were excluded as they did not report the outcome of TIMI flow, did not report admission plasma glucose, or full articles not available. No additional studies were added through the manual search. Therefore, a total of 10 articles met the inclusion criteria from section 2.2 and were included in the meta-analysis. The PRISMA flow diagram is demonstrated in **Figure 1**.

Description of included studies

We extracted data from the 10 included studies as stated in the methods section 2.3. There was no discrepancy in the extracted data by the two investigators. Publication year ranged from year 2008 to 2019 with a total population of 10,991 patients. There were 9 cohort studies (6 prospective and 3 retrospective) and 1 randomized controlled trial. Included studies were conducted in USA, Europe, and Asia. We separated studies into 2 groups based on the definition of AH defined in each study. Studies that use a cutoff value of ≥120 to ≥150 mg/dl will be included in group 1, and studies that use a cutoff value of ≥150 to ≥200 mg/dl will be included in group 2. A summary of study characteristics is shown in **Table 1**.

Quality assessment of included studies

We evaluated quality of the included studies as stated in methods section 2.3 using the NOS scale and the Cochrane Collaboration tool for assessing risk of bias. Newcastle-Ottawa scales of the included studies are described in Supplementary File 2, and the Cochrane Collaboration tool for assessing risk of bias is shown in Supplementary File 3. Quality of the included observational studies was all considered high quality per NOS scale, ranging from to 8 to 9. The assessment of bias of the study by Lonbog et al. were considered low in all bias, including overall bias risk, per the Cochrane Collaboration tool for assessing risk of bias.

Meta-analysis results

Admission hyperglycemia and risk of reperfusion failure: We performed random-effects

Table 1. Study characteristics of the included studies

First author, year	Country	Study design	Total population/ male (n)	Study population	Mean age ± SD	Patients with known DM (%)	Diagnosis of baseline DM	Participants mean HbA1c (%)	Incidence of reperfusion failure (event/total (%))	Definition of AH	Incidence of AH (%)	Glucose measure method (Plasma vs fingerstick)
Ding, 2019	China	Retrospective cohort study	1698/1229	Non-DM patients with STEMI undergoing pPCI	Median; AG≤140: 63, 140<AG<180: 64, ≥180: 66	0	History, A1c>6.5%	Median; AG≤140: 5.6, 140<AG<180: 5.7, ≥180: 5.8	NA	Stratified into multiple groups	28.5%	Plasma
Ekmekci, 2013	Turkey	Prospective cohort study	503/442	Patients with STEMI undergoing pPCI	AG<118: 54.3±12.6, AG=118-145: 55.1±12.4, AG>145: 56.3±12.5	0	History	N/A	39/503 (7.75)	Stratified into multiple groups	38.2% (>145 mg/dl)	N/A
Hoebers, 2012	Netherlands	Retrospective cohort study	1646/1170	Patients with STEMI undergoing pPCI	Median; DM: AG<140: 69, AG=140-198: 71, AG>198: 66 Non-DM: AG<140: 59, AG=140-198: 63, AG>198: 62	13	History	N/A	155/1646 (9.4)	Stratified into multiple groups	76.8% (>140 mg/dl)	Plasma
Kalinczuk, 2018	Poland	Prospective cohort study	323/233	Patients with STEMI undergoing pPCI	60.4±11.5	17	History, previously treated with diet or hypoglycemic agent	N/A	59/323 (18.27)	≥158 mg/dl	44.6%	Plasma
Khalfallah, 2019	Egypt	Prospective cohort study	660/368	Patients with STEMI undergoing PCI	AH: 56.8±10.1, non-AH: 54.7±9.2	0	History, A1c>6.5%	AH: 5.1±0.3, non-AH: 5.0±0.3	138/660 (20.9)	>140 mg/dl	16.8%	Plasma
Lavi, 2008	Israel	Prospective cohort study	431/353	Patients with STEMI undergoing PCI	Non-DM, no AH: 56±12, non-DM, AH: 58±12, DM: 61±11	20.4	History, previously treated with diet or hypoglycemic agent	N/A	52/431 (12)	>126 mg/dl	44% (35% in non-DM)	Plasma
Lonbog, 2014	Denmark	Randomized controlled trial	210/168	Patients with STEMI	61±11	8	History	N/A	21/210 (10)	>149 mg/dl in non-DM, >231 mg/dl in DM	40%	N/A
Planer, 2013	USA	Prospective, open-label study	3602/2612	Patients with STEMI undergoing PCI	Median; AG≤122.4: 58.1, AG122.5-156: 60, AG>156: 62.3	16.6	History, previously treated with diet or hypoglycemic agent	N/A	479/3602 (13.3)	>156 mg/dl	43.7 (>156 mg/dl)	Plasma
Timmer, 2011	Netherlands	Retrospective cohort study	4176/3477	Non-DM patients with STEMI undergoing pPCI	A1c<5.35%: 59±12, A1c=5.36-5.54%: 62±12, A1c=5.55%-5.80%: 63±13, A1c>5.81%: 65±12	0	History, previously treated with diet or hypoglycemic agent	24.5% with A1c>5.8%	365/4176 (8.7)	Stratified into multiple groups	58.2 (>147 mg/dl)	Plasma

Usami, 2009	Japan	Prospective cohort study	2433/1870	Non-DM patients with STEMI undergoing pPCI within 24 hr	non-AH, no ICT: 65.6±11.8, non-AH, ICT: 64±12.4, AH, no ICT: 68.7±11.9, AH, ICT: 68±11.8	0	History, A1c>5.8%, previously treated with diet or hypoglycemic agent	AH: 5.2±0.3, non-AH: 5.1±0.4	265/2433 (10.9)	>200 mg/dl	9.5	Plasma

AG: Admission glucose, AH: Admission hyperglycemia, DM: Diabetes mellitus, ICT: Intra-coronary thrombectomy, N/A: Not applicable, pPCI: Primary percutaneous coronary intervention, STEMI: ST-elevation myocardial infarction, TIMI: Thrombolysis in myocardial infarction.

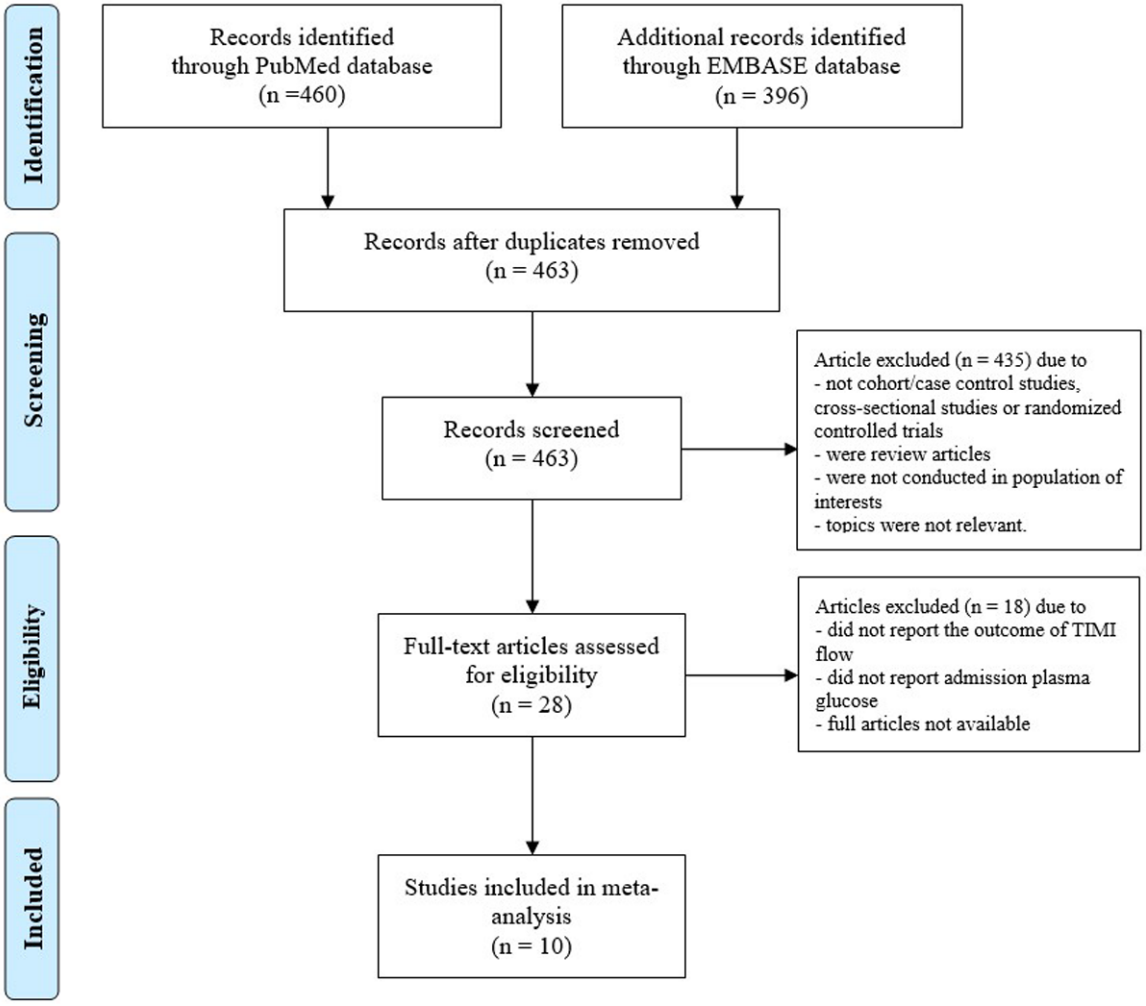

Figure 1. PRISMA flow diagram.

model as stated in methods section 2.5. We found that AH is associated with increased risk of reperfusion failure in both group 1 (pooled OR=1.78, 95% CI: 1.35-2.33, I^2=63.2%, P<0.001) and group 2 (pooled OR=1.44, 95% CI: 1.14-1.82, I^2=57.1%, P<0.001). The forest plot demonstrating the association between AH and risk of reperfusion failure is shown in **Figure 2A**, **2B**.

Subgroup analysis: We performed a subgroup analysis of non-diabetic patients. In subgroup analysis of non-diabetic patients, we found that AH is also associated with increased risk of reperfusion failure in both group 1 (pooled OR=1.81, 95% CI: 1.29-2.54, I^2=69.8%, P< 0.001) and group 2 (pooled OR=1.61, 95% CI: 1.17-2.21, I^2=55.2%, P<0.001). The forest plots of the subgroup analysis of non-diabetic patients are shown in **Figure 3A**, **3B**.

Sensitivity analysis: To assess the stability of the results of the meta-analysis, we conducted a sensitivity analysis for each outcome by excluding one study at a time as stated in methods section 2.5. For every outcome, none of the results were significantly altered, as the results after removing one study at a time were similar to that of the main meta-analysis, indicating that our results were robust.

Publication bias: We aimed to investigate potential publication bias via funnel plot and Egger's test as stated in methods section 2.5. However, as we only have up to nine studies in any analysis, the number is insufficient to reject

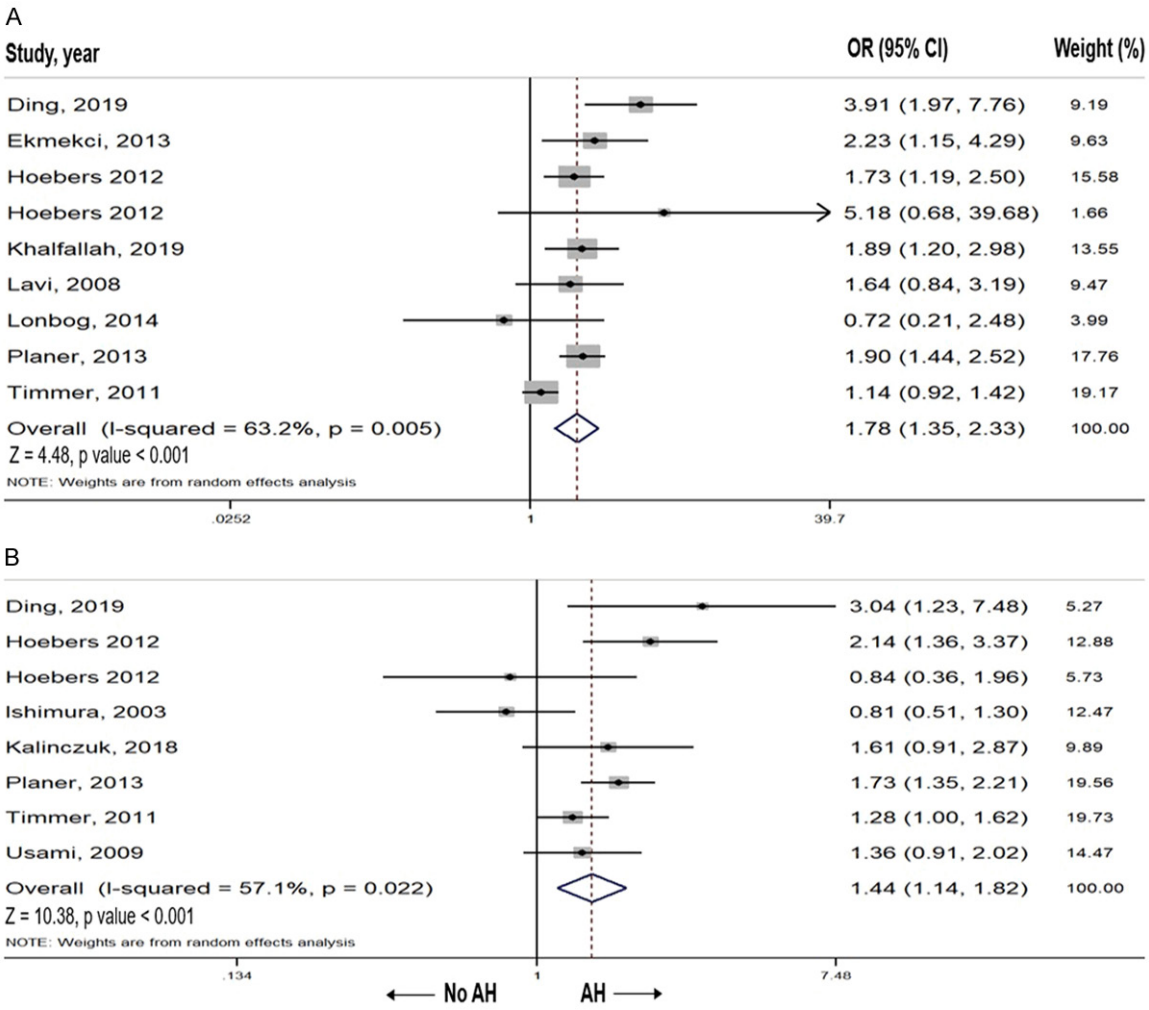

Figure 2. Forest plot demonstrating the association of admission hyperglycemia and risk of reperfusion failure in patients presented with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention; A: Group 1, B: Group 2.

the assumption of no funnel plot asymmetry. Thus, we did not perform a funnel plot or Egger's test [27, 28].

Discussion

Our meta-analysis demonstrated that AH is strongly associated with an increased risk of reperfusion failure in this population. The association persists despite different glucose cutoff value, including the non-diabetic population.

Diabetes mellitus is widely known to be associated with coronary artery disease (CAD) along with an increased risk of major adverse cardiac events, such as acute coronary syndrome (ACS) [29, 30]. However, a review of literature has shown that even in the absence of diabetes, hyperglycemia in the setting of ACS is associated with worse clinical outcomes and increased mortality, both in the immediate post-PCI period and during long-term follow-up [31-34]. Some studies described that outcomes are worse in those without diabetes [35], while others suggested the opposite [32, 36]. One particular outcome of interest is reperfusion failure following pPCI. There is evidence suggesting that hyperglycemia at presentation may be an important predictor for reperfusion failure in patients undergoing pPCI [15, 37].

The literature on the management of hyperglycemic in critically-ill patients is lacking. Berghe G et al. initially reported in the Leuven Surgical trial that intensive glycemic control with a goal

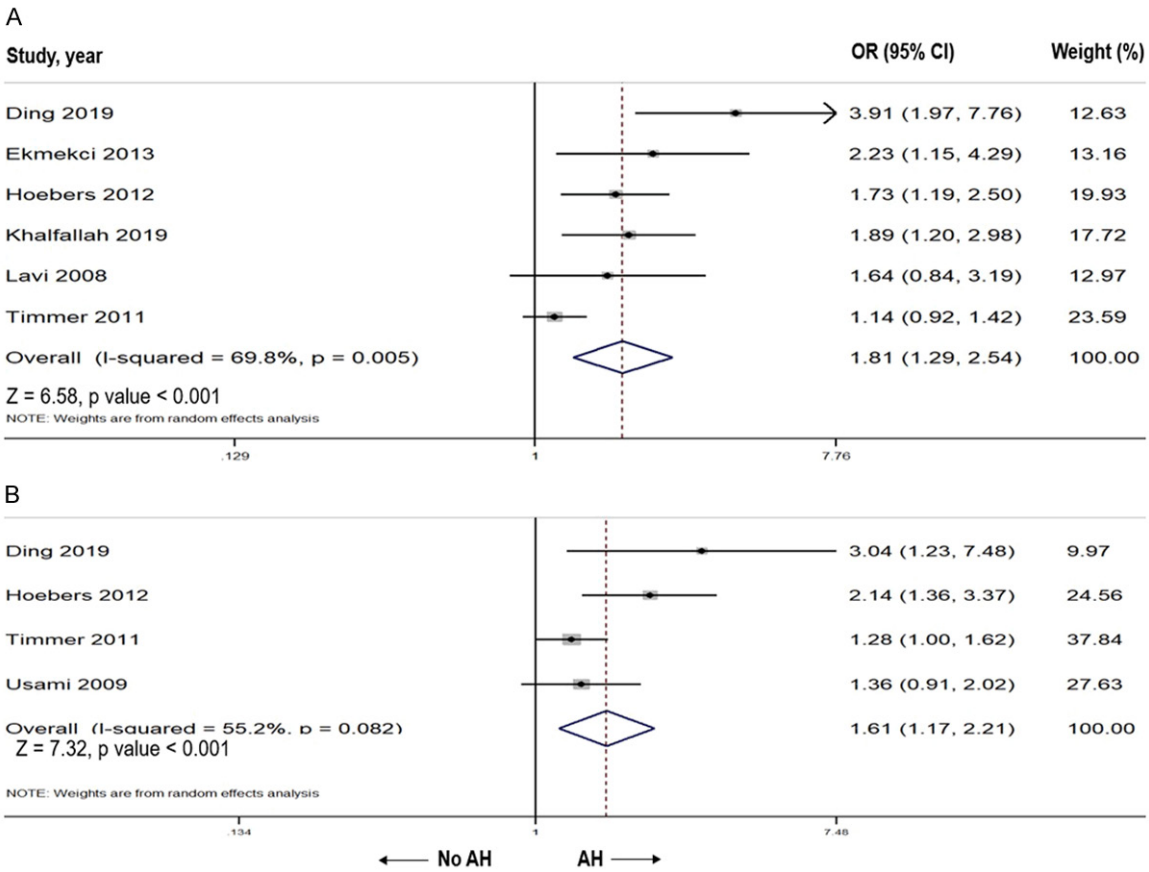

Figure 3. Forest plot demonstrating the association of admission hyperglycemia and risk of reperfusion failure in patients presented with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention, subgroup analysis of non-diabetic patients; A: Group 1, B: Group 2.

of 80-110 mg/dl significantly lower mortality in the surgical intensive care unit (ICU) compared to conventional goal of 180-200 mg/dl [38]. However, these results were not replicated in the medical ICU in the Leuven Medical Trial [39]. A larger multicenter trial, The Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) trial, later demonstrated that intensive glycemic control in medical ICU with a target of 81-108 mg/dl led to increased mortality when compared to conventional target of ≤180 mg/dl [40]. Many other trials have been performed, which have failed to show mortality benefit in patients controlled to both glucose level <110 mg/dL or <180 mg/dL [41]. Despite these results, patient population in mentioned studies differs significantly from our population of interests. As of now, there is a paucity of evidence regarding the effect of glucose control prior to pPCI in STEMI patients or in cardiac care unit (CCU). The 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation recommends to evaluate glucose levels in all STEMI patients regardless of diabetic status, and to monitor more glucose more frequent in any patient with hyperglycemia, while attempting to maintain a goal of <200 mg/dl [19]. The 2013 ACCF/AHA guideline for the management of ST-Elevation myocardial infarction similarly recommends controlling blood glucose level below 180 mg/dl while avoiding hypoglycemia [20]. Both guidelines did not mention any usage of hyperglycemia for ACS risk stratification and did not provide recommendations regarding the therapeutic management of hyperglycemia pre-procedure.

To the best of our knowledge, this is the first meta-analysis examining the association between AH and the risk of reperfusion failure in STEMI patients undergoing pPCI. This meta-

analysis consists of eleven studies involving 16,674 patients admitted to hospital with a diagnosis of STEMI all underwent pPCI. The included studies used different cut off values for hyperglycemia, with most using a range of >120 mg/dl to >150 mg/dl, while the rest used a higher cut-off of >150 mg/dl to >180 mg/dl. Thus, we separated study population into 2 groups based on the cutoff values for hyperglycemia (>120 mg/dl to >150 mg/dl VS >150 mg/dl to >180 mg/dl.) and performed separate analysis. We also performed a subgroup analysis of nondiabetic patients. We use TIMI flow grade following pPCI of <3 to defined reperfusion failure, which is uniform across the included studies.

Five studies individually demonstrated a statistical significance association between AH and increased risk of reperfusion failure. The other six studies suggested a positive correlation but did not reach statistical significance. Nevertheless, the pooled OR reached statistical significance for both group 1 (pooled OR=1.78) and group 2 (pooled OR=1.44). Interestingly, the strength of association for group 2 (PH defined as >150 mg/dl to >180 mg/dl) appeared to be lower than group 1, indicating a lack of an exposure-response relationship beyond a certain level. However, as the 95% CI overlaps, we could not draw any conclusions in comparing the strength of the association between the 2 groups.

In addition, we performed a subgroup analysis of patients without DM. Seven of the studies involving 6,609 patients were included in this subgroup analysis. We were able to capture data pertaining to non-diabetic patients, since we relied on studies that either reported specific data that excluded diabetic patients or studies that reported non-diabetic and diabetic results separately. We used the same glucose cutoff value as the main analysis. Results clearly demonstrate that even in the absence of diabetes, hyperglycemia alone is a significant risk factor for reperfusion failure. The strength of the association was similar to the main analysis for both glucose cutoff values.

The mechanism behind this relationship is poorly understood. Recent studies suggested that hyperglycemia may be associated with hindered microvascular function as well causing augmenting thrombosis leading to microvascular thrombi and impaired reperfusion [34, 36]. It should also be considered that hyperglycemia may simply be a consequence of acute stress from severe ACS rather than a cause. Larger infarcts have been shown to be associated with hyperglycemia, which were likely from a greater catecholamine release and increased stress response [42, 43]. In this case, the presence or absence of hyperglycemia will be useful as a marker for ACS severity and for prognostication. Nevertheless, further research is needed to delineate whether hyperglycemia is a cause or consequence of worse outcome in ACS.

In this systematic review and meta-analysis, we present strong evidence that AH is associated with an increased risk of reperfusion failure in STEMI patients undergoing pPCI, regardless of diabetic status. Despite not being able to establish causation, we would like to raise awareness and strongly encourage physicians to be cautious and recognize AH as a risk factor for reperfusion failure and worse outcome in patients presenting with STEMI. Glucose control post-cardiac procedure, including PCI and CABG, is essential and is being routinely practiced per standard guideline. However, there is no strong evidence whether strict blood glucose in patients with AH prior to pPCI reduces the risk of reperfusion failure, or could potentially cause harm. We recognize this as a future area of research; to evaluate the potential clinical outcomes of correction of AH prior to pPCI in STEMI population.

The strengths of our meta-analysis come primarily from the inclusion of a large number of studies and robust patient population. While many of the individual studies lacked the power to achieve a statistically significant result, our pooled analysis was able to demonstrate a significant association between AH and the increased risk of reperfusion failure following pPCI in STEMI population. We also acknowledged several limitations as well. Firstly, the extracted data used in the meta-analysis were not adjusted for confounders. Secondly, though we intended to perform subgroup analysis of diabetic patients, there were not sufficient data from the included studies to perform analysis of this subgroup. Thirdly, we found significant heterogeneity in our analysis, which is likely secondary to demographic differ-

ences and different glucose cutoff value. Moreover, we used TIMI flow as our main measurement for reperfusion failure and did not use other methods such as resolution of ST-segment or myocardial blush grade. Thus, this will only measure the epicardial flow and would not detect microvascular dysfunction or impaired myocardial perfusion.

Conclusions

In this systemic review and meta-analysis, we have demonstrated that AH is associated with an increased risk of reperfusion failure in STEMI patients undergoing PCI, irrespective of diabetic status. Clinicians should strongly consider hyperglycemia as a prognostic factor in patients presenting with STEMI. Further studies are needed to assess the potential benefit of glucose control prior to pPCI in this population.

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Disclosure of conflict of interest

None.

Abbreviations

AH, Admission hyperglycemia; OR, Odds ratio; pPCI, primary percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

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Supplementary File 1. Search term.

PUBMED

("hyperglycaemia" [All Fields] or "hyperglycemia" [MeSH Terms] or "hyperglycemia" [All Fields]) and ("percutaneous coronary intervention" [MeSH Terms] or ("percutaneous" [All Fields] and "coronary" [All Fields] and "intervention" [All Fields]) or "percutaneous coronary intervention" [All Fields]).

("hyperglycaemia" [All Fields] or "hyperglycemia" [MeSH Terms] or "hyperglycemia" [All Fields]) and ("myocardial reperfusion" [MeSH Terms] or ("myocardial" [All Fields] and "reperfusion" [All Fields]) or "myocardial reperfusion" [All Fields] or ("coronary" [All Fields] and "reperfusion" [All Fields]) or "coronary reperfusion" [All Fields]).

EMBASE

('hyperglycemia percutaneous coronary intervention' or (('hyperglycemia'/exp or hyperglycemia) and percutaneous and coronary and ('intervention'/exp OR intervention))) and ([article]/lim or [article in press]/lim).

('hyperglycemia coronary reperfusion' or (('hyperglycemia'/exp or hyperglycemia) and coronary and ('reperfusion'/exp or reperfusion))) and ([article]/lim or [article in press]/lim).

Supplementary File 2. Newcastle-Ottawa scale of the included studies

First author, year	Selection				Comparability	Outcome			Total score
	Representativeness	Selection of the non-exposed cohort	Ascertainment	Endpoint not present at start	Comparability (Confounding)	Assessment of outcome	Follow-up duration	Adequacy follow-up	
Ding, 2019	*	*	*	*	*	*	*	*	8
Ekmekci, 2013	*	*	*	*	*	*	*	*	8
Hoebers, 2012	*	*	*	*	**	*	*	*	9
Kalinczuk, 2018	*	*	*	*	**	*	*	*	9
Khalfallah, 2019	*	*	*	*	**	*	*	*	9
Lavi, 2008	*	*	*	*	**	*	*	*	9
Planer, 2013	*	*	*	*	*	*	*	*	8
Timmer, 2011	*	*	*	*	*	*	*	*	8
Usami, 2009	*	*	*	*	**	*	*	*	9

Notes: The Newcastle-Ottawa scale uses a star system (0 to 9) to evaluate included studies on 3 domains: selection, comparability, and outcomes. Star (*) = item presents. Maximum 1 star (*) for selection and outcome components and 2 stars (**) for comparability components. Higher scores represent higher study quality.

Supplementary File 3. The Cochrane Collaboration tool for assessing risk of bias of the included randomized controlled trial

First author, year	Selection bias		Performance bias	Detection bias	Attribution bias	Reporting bias	Other bias	Overall bias risk
	Random sequence generation	Allocation concealment						
Lonbog, 2014	Low	Low	Low	Low	Low	Low	Low	Low