The Value of Epicardial Adipose Tissue for the Patients Treated with Percutaneous Coronary Intervention: A Systemic Review and Meta-analysis

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Research article

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Abstract

Background

Accumulating evidences suggest that the prognostic value of epicardial adipose tissue (EAT) on no-reflow, in-stent restenosis (ISR), infarct size, and main adverse cardiovascular events (MACE) for the patients treated with percutaneous coronary intervention (PCI). The relationship between EAT and outcomes of patients underwent PCI is still partly elusive.

Methods

To elucidate the relationship in detail, we searched PubMed, web of science, and the Cochrane Library for studies evaluating the association of EAT and patients treated with PCI. Thirteen studies enrolling 3683 patients were eventually include in our systemic review and meta-analysis.

Results

The EAT measured by thickness or volume was significantly higher in the ISR group compared to those in the non-ISR group (The standard mean difference -0.34, 95% CI, -0.49, -0.18, $p < 0.0001$; $I^2 = 36\%$). The incidence of no-reflow was significantly higher in thicker EAT group compared to thin EAT group (pooled relative ratio 1.52, 95%CI 1.29-1.80, $p < 0.0001$; $I^2 = 0\%$). Thicker EAT was significantly associated with MACEs (pooled relative ratio 1.50, 95% 1.18-1.90, $p = 0.008$). A lower EAT volume is associated with larger infarct size in ST elevated myocardial infarction patients treated with primary PCI (standard mean difference was -5.45, 95% CI -8.10, -2.80; $p < 0.0001$; $I^2 = 0\%$). In summary, our systemic review and meta-analysis suggest that high EAT is related with a significant increased risk of non-reflow, MACE and decreased infarct size in patients with coronary artery disease treated with PCI. This paradox phenomenon demonstrates that the quality of EAT may play more important role than the solely thickness or volume of EAT.

1. Background

Percutaneous coronary intervention (PCI) is one of the major revascularization strategy for coronary artery disease (CAD), especially the ST segment elevated myocardial infarction (STEMI) [1]. PCI can effectively optimize coronary reperfusion and alleviate ischemic pains, then significantly reduce the mortality and improve the quality of patients' life[2]. However, some complications continually perplex the management of PCI, such as the no-reflow, infarct size reduction, in-stent restenosis (ISR) and main adverse cardiovascular events (MACE)[3].

Accumulating evidences suggest that the prognostic value of epicardial adipose tissue (EAT) on no-reflow, ISR, infarct size and MACE for the patients treated with PCI[4, 5]. previous meta-analysis has been demonstrated that elevated location-specific EAT thickness at the left atrioventricular groove is associated with obstructive coronary artery disease[6]. EAT, directly deposited around the myocardium and epicardial segments of the coronary arteries, has key roles in the adjustment of cardiovascular or systemic physiology and pathophysiology[7]. By autocrine and paracrine means, it generates various types of anti-/pro-inflammatory mediators and free fatty acids[8]. More recently, multiple clinical researches have shown that increased EAT deposition plays a pivotal role in the development and progression of ISR[9–14], no-reflow[15–18], infarct size[19, 20] or MACE[4, 5, 13, 14] for patients treated with PCI with inconsistent results.

The relationship between EAT and ischemic heart disease might be complex biphasic[21, 22]. Some studies have demonstrated that relationship between larger EAT volume, increased release of inflammatory molecules, and more advanced stages of coronary heart disease[4, 5, 13, 14]. However, patients with cardiomyopathy with left ventricular ejection fraction $< 35\%$ had apparently smaller EAT volume in comparison with healthy controls[22, 23]. Therefore, there exists a paradox between EAT and cardiovascular outcomes in different conditions.

Despite many published articles on the relationship between EAT and outcomes of patients underwent PCI, to the best of our knowledge, the relationship is still partly elusive. Therefore, the present systemic review and meta-analysis was conducted to bridge knowledge gap with the aim of gathering evidences evaluating the prognostic value of EAT for patients underwent PCI. We first briefly overview the relationship of EAT with ISR, and no-reflow. We then move to present key published researches evaluating MACE related with EAT for patients treated with PCI, and discuss remaining challenges.

2. Methods

2.1 Search strategy and selection criteria

We did this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[24].

We searched scientific literature databases for human studies evaluating the value of EAT for patients treated with PCI. We did a systematic search of PubMed, web of science, and the Cochrane Library, using various combinations of keywords such as "epicardial adipose tissue", "epicardial fat", "percutaneous coronary intervention", "Coronary Angioplasty" and "coronary intervention" for eligible studies published up to September 16, 2020. Studies written in English were considered for inclusion; no other languages were allowed.

After initial screening of title and abstracts of the potentially relevant studies, full-texts review of those studies considered relevant were evaluated for eligibility. Criteria for including researches into the systemic review were as follows: (1) studies that involved patients who underwent PCI for any indication (primary PCI, selective PCI, etc.), and (2) studies that reported the association between EAT and outcomes specific to PCI management or MACE. Studies not mentioned the revascularization of PCI were totally excluded. We also searched conference abstracts that reported data relevant to our research question. On the other hand, case reports were excluded. Two reviewers (TX and MX) independently estimated studies for eligibility.

2.2 Data extraction

Two reviewers (TX and MX) independently extracted data from the included full-text studies and entered the data into electronic datasheets. They then extracted information about last name of first author, publication year, study design, sample size, demographics, the methods of EAT measurements, the level of EAT and clinical outcomes. Any discrepancies were resolved by consensus with the two aforementioned reviewers, if necessary, after contact with related authors.

2.3 Outcomes and definitions

In this systemic review and meta-analysis, the outcomes included ISR, no-reflow, infarct size and MACE. There existed subtle heterogeneity of clinical outcomes and events in categories, such as ISR, no-reflow and MACE. Then we listed all the information related the definition in detail. Additionally, the quantification of EAT and measurement methods exists some distinct difference, such as echocardiographic EAT thickness, or EAT volume measured by computed tomography (CT) or cardiac magnetic resonance (cMR). Therefore, all the aforementioned heterogeneities may attenuate the meta-analysis's efficacy. Therefore, we report the detail of every included study to the greatest extent.

2.4 Statistical analysis

Abstracted data from included studies were entered into RevMan 5.3 statistical software (Cochrane Collaboration, Oxford, UK). All the potentially cites of the systemic review and meta-analysis were sorted by the EndNote software. The I^2 statistic was used to test heterogeneity, and the studies were pooled using fixed effects models with low heterogeneity ($I^2 < 50\%$). Otherwise, a random-effects model was used. [25] Risk ratio (RR) was used to pool outcomes with a two-sided significance level of 5 %. Moreover, we also summarized the data as the standard mean difference (SMD) of continuous variables with 95% CIs when the eligible studies presented related information. Individual trial and summary results are reported with 95 % confidence intervals (CI). We assessed the quality of the studies using the Newcastle-Ottawa Scale (NOS). [26] Sensitivity analysis was conducted to determine if an individual study was responsible for the observed effect by omitting one study and the risk of publication bias was assessed by examining the funnel plots. Statistical test was two-tailed with $p < 0.05$ chosen at the level of significance.

3. Results

Systemic review of the database retrieved 248 citations. Lots of papers were excluded based on titles and/or abstract due to clearly not relevant. Then 19 potentially appropriate papers included for full text review. According to the inclusion criteria, 13 studies enrolling 3683 patients were eventually include in the systemic review and meta-analysis. One close related study was presented by oral abstract [15]. Systematic review flow chart is depicted in Figure 1. Interestingly, one paper simultaneously evaluated the relationship of ISR and MACE with EAT for patients underwent PCI [13]. Other two studies recruiting the same patients cohort evaluated the influence of EAT on no-reflow, ISR and MACE, respectively [14, 18]. The other 4 studies solely showed the relationship between EAT and ISR of patients treated with PCI [9-12]. The impact of EAT on MACEs for patients treated PCI was evaluated in other 2 studies [4, 5]. Two studies lonely measured the influence of EAT on no-reflow of patients with STEMI treated with primary PCI [15, 17]. Two studies had demonstrated the relationship between EAT measured by cMR and infarct size for STEMI patients treated with primary PCI [19, 20].

3.1 Description of included studies and quality assessment

The baselines of included studies' characteristics are summarized in Table 1a, 1b, 1c and 1d. Average age across all studies 58 years, 77% of patients were male. According to the included criteria, the patients of all the included studies were treated with PCI for revascularization. Seven studies totally involved 1677 STEMI/non-STEMI patients explicitly mentioned that the revascularization strategy was primary PCI [9, 13-15, 18-20].

Study quality, shown in table 2, was relatively high. Based on the NOS quality assessment, 4 studies were defined as high quality (2 study scored 8 and 5 studies scored 7), and the other 6 studies were defined as moderate quality (4 studies scored 6 and two studies scored 5).

Table 1a
Study and participant summary characteristic on in-stent restenosis.

Trials on ISR	Study design	Population	number of patients	Mean age (years)	Male (%)	EAT measurement methods	Definition of ISR	EAT thickness(mm)/volume (ml)(ISR VS non-ISR)	Median/mean follow-up
Cabrera-Rego 2019 ⁸	Prospective	STEMI	169	62.9±10	67.3	Echocardiography/EAT thickness	≥ 50% luminal diameter narrowing	5.51 ± 1.6 VS 4.14 ± 2.0 (P=0.06)	1 year
ZHOU 2016 ⁹	Retrospective	CAD	364	61.1±12.1	90.9	CT/ EAT volume	≥ 50% luminal diameter narrowing	154.5 ± 74.6 VS 131.0 ± 52.2 (P=0.008)	12.7 months
Park 2013 ¹⁰	Prospective	CAD	407	59±11	72.8	Echocardiography/EAT thickness	target lesion revascularization	3.8 ± 1.8VS 3.2 ± 1.9 (P=0.002)	12 months
Nikaeen 2011 ¹¹	Retrospective	CAD	117	57.6 ± 9.6	60.7	Echocardiography/EAT thickness	≥ 50% luminal diameter narrowing	4.4 ± 1.8VS4.52 ± 1.9 (P=0.8)	1 year
Park 2016 ¹²	Prospective	STEMI	761	57 ± 12	80.7	Echocardiography/EAT thickness	Target lesion revascularization	/	46 months
Zencirci 2015 ¹³ a	Prospective	STEMI	114	54 ± 10	86.8	Echocardiography/EAT thickness	Target-vessel revascularisation	/	3 year
ISR, in-stent restenosis; EAT, epicardial adipocyte tissue; STEMI, ST segment elevated myocardial infarction; CAD, coronary artery disease.									

Table 1b
Study and participant summary characteristic on no-reflow.

Trials on no-reflow	Study design	Population	number of patients	Mean age (years)	Male (%)	EAT measurement methods	EAT thickness(mm) No-flow VS normal	Definition of no-reflow
Cerit.2018 ¹⁴	retrospective	STEMI	249	/	/	Echocardiogram/EAT thickness	/	/
Bakirci 2015 ¹⁶	Prospective	STEMI	229	54.3 ± 10.1	77.7	Echocardiogram /EAT thickness	6.4±0.9vs5.5±1.3 (p<0.001)	Postprocedural TIMI flow grade
Zencirci 2014 ¹⁷	Prospective	STEMI	114	54 ± 10	86.8	Echocardiogram /EAT thickness	5.4 ± 2 VS3.9 ± 1.7 P=0.001	Patients with ΔSTR < 70 % were accepted as no-reflow phenomenon group
EAT, epicardial adipocyte tissue; STEMI, ST segment elevated myocardial infarction; ΔSTR, the difference between two measurements was accepted as resolution of the sum of ST-segment elevation and expressed as ΔSTR (Measurements were obtained from the first ECG, recorded on admission and a second ECG recorded after successful primary angioplasty.)								

Table 1c
Study and participant summary characteristic on main adverse cardiovascular events.

Trials on MACEs	Study design	Population	number of patients	Mean age (years)	Male (%)	EAT measurement methods	Definition of MACEs	Median follow-up
Lu 2019 ⁴	Prospective	CAD	500	58.9	59.2	CT/EAT volume	death, myocardial infarction, and revascularization	25.2 months
Tscharre 2017 ⁵	Prospective	ACS	438	62.6±13.5	66.9	Echocardiogram/EAT thickness	cardiovascular death, non-fatal myocardial infarction and non-fatal stroke	3 years
Park 2016 ¹²	Prospective	STEMI	761	57 ± 12	80.7	Echocardiogram/EAT thickness	all-cause death, recurrent myocardial infarction and target vessel revascularisation.	46 months
Zencirci 2015 ¹³	Prospective	STEMI	114	54 ± 10	86.8	Echocardiogram/EAT thickness	cardiac death, non-fatal myocardial infarction, target vessel revascularisation, or admission for heart failure	3 years
EAT, epicardial adipocyte tissue; STEMI, ST segment elevated myocardial infarction; CAD, coronary artery disease; ACS, acute coronary syndrome; MACEs, main adverse cardiovascular events;								

Table 1d
Study and participant summary characteristic on related with infarct size.

Trials on infarct size	Study design	Population	number of patients	Mean age (years)	Male (%)	EAT measurement methods	Infarct size (% LV mass) (EAT low vs high)
Gohbara 2016 ¹⁸	Prospective	STEMI	142	64 ±12	85.0	CMR/EAT volume	25± 10 vs19±10 ^a p<0.01
Bière 2017 ¹⁹	Prospective	STEMI	193	58±12	85.5	CMR/EAT volume	23 ± 13.7 VS 18.3 ± 11.9 ^b p=0.041
EAT, epicardial adipocyte tissue; STEMI, ST segment elevated myocardial infarction; ^a .low and high group Patients belonging to the lower tertile of EAT volume were categorized into the low EAT group (group L) and the other two-thirds into the high EAT group (group H); ^b . quartile 1 st VS quartile 4 th							

Table 2
Assessment of study quality.

Reference	Quality Indications of Newcastle-Ottawa Scale Total								Total
	1	2	3	4	5	6	7	8	
Cabrera-Rego 2019 ⁸	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
ZHOU 2016 ⁹	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7
Park 2013 ¹⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Nikaeen 2011 ¹¹	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Park 2016 ¹²	Yes	Yes	No	Yes	No	Yes	Yes	Yes	6
Zencirci 2015 ¹³ a	No	Yes	Yes	Yes	Yes	Yes	No	No	5
Cerit.2018 ¹⁴	Yes	Yes	No	Yes	No	No	Yes	Yes	5
Bakirci 2015 ¹⁶	No	Yes	Yes	Yes	Yes	Yes	Yes	No	6
Zencirci 2014 ¹⁷	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Lu 2019 ⁴ a	No	Yes	Yes	Yes	Yes	Yes	No	Yes	6
Tscharre 2017 ⁵ b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Gohbara 2016 ¹⁸	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	7
Bière 2017 ¹⁹	Yes	Yes	No	Yes	Yes	No	Yes	Yes	6
1. Representativeness of the exposed cohort; 2. Selection of the non-exposed cohort; 3. Ascertainment of exposure; 4. Demonstration that outcome of interest was not present at start of study; 5. Comparability of cohorts on the basis of the design or analysis; 6. Comparability of cohorts on the basis of the design or analysis; 7. Was follow-up long enough for outcomes to occur; 8. Adequacy of follow up of cohorts									

3.2 Quantitative data synthesis

The value of EAT for ISR

There are totally 6 studies evaluated the value of EAT for the ISR[9-14]. The EAT measured by thickness or volume was significantly higher in the ISR group compared to those in the non-ISR group. The standard mean difference was -0.34 estimated in 4 studies[9-12](95% CI, -0.49, -0.18)p<0.0001; I²=36%) (Fig. 2a). However, the value of EAT was not associated with the incidence of ISR when evaluated in five include studies[9-11, 13, 14] (pooled RR 1.23, 95%CI 0.97-1.56, p=0.09; I²=82%) (Fig. 2b). The discrepancy may partly due to the distinct heterogeneity of included studies and the different definition of ISR.

The value of EAT on no-reflow

The incidence of no-reflow was significantly higher in thicker EAT group compared to thin EAT group (pooled RR 1.52, 95%CI 1.29-1.80, p<0.0001; I² =0 %) (Fig.3a). In the meanwhile, the EAT thickness was higher in the non-reflow group than those in the normal reflow group (SMD -0.94,95%CI, -1.41, -0.47, p<0.001; I² =64%) (Fig. 3b).

The prognostic value of EAT on MACEs

There were totally 4 studies[4, 5] included 1813 CAD patients showed thicker EAT was significantly associated with MACE (pooled RR 1.50, 95% 1.18-1.90, $p=0.008$) (Fig4). Although these data were not statistically heterogeneous ($I^2=0\%$), yet the definition varied between included studies.

Relationship between EAT and infarct size

Two eligible studies[19, 20] included 335 STEMI patients treated with primary PCI reported the relationship between EAT volume and infarct size, which are both measured by cMR. There was no heterogeneous ($I^2=0\%$) between the two studies. The SMD was -5.45 (95% CI -8.10, -2.80; $p<0.0001$) (Fig5). This suggested that a lower EAT volume is associated with larger infarct size in STEMI patients treated with primary PCI.

3.3 Heterogeneity among Included Studies

Five included studies, evaluated the relation between EAT and ISR, exist evident heterogeneous which may partly due to the difference definition of ISR. The other main studies have minor or no heterogeneity shown in the aforementioned forest plot. Unfortunately, due to the small number of included studies, we could not explore the detail sources of heterogeneity with subgroup analysis or meta-regression.

3.4 Publication Bias and Funnel Plots

The statistical assessment of publication bias was not found in the main comparison outcomes. The funnel plots showed each comparison outcomes in detail (Supplement S1a, S1b, S1c and S1d).

3.5 Sensitivity analyses

To analyze sensitivity, the primary results were not influenced by omitting one study. However, comparison between EAT and infarct size only contains two studies, so the sensitivity analysis can't perform. (Supplement S2a, S2b, S3 and S4)

4. Discussion

In this systemic review and meta-analysis including 13 studies in the era of PCI, we demonstrated high EAT is associated with a statistically significant increased risk of non-reflow, MACEs and decreased infarct size in patients with CAD. However, EAT was not clearly associated with ISR.

EAT was shown to be more than a simple adipose tissue depot, since it is recognized as an extraordinarily active endocrine organ. Then it may have either a beneficial or detrimental effect depending on the homeostasis[27]. Accumulated evidences suggest that EAT secretes anti/pro-inflammatory hormones and cytokines which play dual pro-atherogenic and anti-atherogenic roles in the pathogenesis of coronary atherosclerosis[28]. EAT was also recognized as a metabolic transducer role in coronary artery disease[29]. More and more studies shown EAT plays a pivotal role in the outcomes of CAD patients in the era of PCI, such as the infarct size, non-reflow and ISR. In this meta-analysis thicker EAT was related with some detrimental effects, for example non-reflow and MACEs.

Inflammation mediated by neutrophil activation was shown to have an undeniable role in the pathogenesis of no-reflow phenomenon[30]. Takaoka et al found that endovascular injury induces rapid and marked changes in perivascular adipose tissue, mainly mediated by TNF- α [31]. EAT may secrete more pro-inflammatory factors to induce the no-reflow. In this meta-analysis, the effect pooled from 3 studies included STEMI patients treated with primary PCI demonstrated that the incidence of no-reflow was significantly higher in thicker EAT group, possibly due to EAT's pro-inflammatory role activated by coronary injury.

The mechanisms of ISR are complex, due to its affected by multi-factor[32]. The factors may involve clinical (senior, sex, diabetes mellitus, dyslipidemia, obesity and smoking), angiographic factors (proximal lesions, PCI on the main left coronary artery, arteries of small diameter, long stenosis, use of bare metal stents) and factors inherent to the procedure (neointimal hyperplasia, mural thrombus)[32]. Many studies demonstrated that higher EAT was significantly associated with ISR[9–14]. Interestingly, this meta-analysis shown that the association between EAT and ISR may not clear, although the ISR groups had higher EAT. This may partly due to the complex of ISR and the bidirectional relationship between EAT and CAD[22]. Further studies are needed to elucidate the relationship between EAT and ISR.

Despite the different definition of MACEs in this meta-analysis, the pooled results also demonstrated that higher EAT was associated with worse outcomes. In the meanwhile, this results may be confirmed by recent study aimed at investigating the effect of statins on EAT[33]. EAT is a new target for statin therapy, and statin's effect on EAT size and phenotype may be strongly involved in beneficial cardiovascular outcomes in statin-treated patients[34].

Epicardial adipose tissue volume is not a simple marker of coronary artery disease[35]. Although the thicker or higher volume EAT may have detrimental effect on cardiovascular outcomes as the aforementioned results, yet it is interesting to note that high EAT was paradoxically associated with less infarct size and acted as an effect modifier in the relation between the extent of infarct size[36]. The results were in accordance with the other study[37]. Correspondingly, the meta-analysis also demonstrated that a lower EAT volume is associated with larger infarct size. This suggests that EAT may have a cardioprotective effect in

a specific condition, such as acute myocardial infarction. Potential benefits might be associated with local hormonal release of adiponectin, or to the fact that EAT may be serving as an energy reservoir in the condition of acute myocardial infarct[38].

Coincidentally, obese patients also have thicker EAT. Recently large meta-analyses of patients with acute myocardial infarction have shown that patients in the overweight and obese groups have lower short-term and long-term all-cause mortality compared with patients in the normal weight group[39, 40]. Franssens et al's finding supported that EAT radiodensity may be a more sensitive marker than EAT volume. Some studies have shown that higher expression levels of uncoupling protein 1, a brown adipose tissue specific protein, in EAT compared to other adipose tissue depots[41]. This may suggest human EAT exists brown adipocytes or brite/beige cells at adult stage[7]. It is likely that increasing the brite/beige cells in white adipose tissue might also have greater metabolic benefits[42]. This urges us to determine the quality of EAT rather than the solely thickness or volume of EAT. Recently, Yu Du and his colleagues have shown that lesion-specific EAT volume index, but not density, seems positively and independently associated with myocardial ischemia[43]. In some way, quantification of epicardial fat using 3D cine Dixon MRI may play a pivotal role in determining the quality of EAT[44].

The present study must be interpreted within the context of its potential limitations. Firstly, the number of included studies is relatively small. Secondly, heterogeneity: There was significant heterogeneity among EAT and ISR or reflow. However, as a result of the limited number of included studies for each outcome, we couldn't precisely identify the sources of heterogeneity. Thirdly, the included studies have not the same criteria for ISR and MACEs, which may have substantial detrimental on the explanation of the pooled results. Fourthly, the included studies are mainly prospective study, partially hindering the explanation of the causation and effect between EAT and relative events.

5. Conclusions

Our systemic review and meta-analysis suggest that high EAT is related with a significant increased risk of non-reflow, MACEs and decreased infarct size in patients with CAD treated with PCI. This paradox phenomenon demonstrates that the quality of EAT may play more important role than the solely thickness or volume of EAT.

Abbreviations

EAT, epicardial adipose tissue;

ISR, in-stent restenosis;

MACE, main adverse cardiovascular events;

PCI, percutaneous coronary intervention;

CAD, coronary artery disease;

STEMI, segment elevated myocardial infarction;

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis;

CI, confidence intervals;

SMD, standard mean difference;

CT, computed tomography;

cMR, cardiac magnetic resonance;

NOS, Newcastle-Ottawa Scale;

SMD, standard mean difference;

RR, Risk ratio;

Declarations

Ethics approval and consent to participate Consent for publication Availability of data and material

All the included studies have appropriate ethics approval and consent. All the data and material will be available by contacting the corresponding author. All authors approved the manuscript for submission to the journal.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceived and designed the systemic review and meta-analysis: TX and MX. Analyzed the data: TX. Wrote the paper: TX and MX. All authors read and approved the final manuscript.

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Figures

Figure 1

Flowchart of study selection process to determine the studies to be included in the meta-analysis.

Figure 2

(A) Forest plot evaluated the impact of EAT divided by ISR vs non-ISR. (B) Forest plot evaluated the value of EAT for ISR.

Figure 3

(A) Forest plot evaluated EAT for no-reflow. (B) Forest plot evaluated EAT divided by no-reflow and normal reflow.

Figure 4

Forest plot evaluated EAT for MACE.

Figure 5

Forest plot evaluated EAT for infarct size.

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