

## Review Article

# Effect of metformin on cardiac function in patients with STEMI: a systematic review and meta-analysis

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**Abstract:** *Background and aim:* Metformin may have the potential in improving cardiac function in patients with ST-elevation myocardial infarction (STEMI). However, the results remain controversial. We conducted a systematic review and meta-analysis to explore the effect of metformin on cardiac function of patients with STEMI. *Methods:* PubMed, Embase, Web of science, EBSCO, and Cochrane library databases were systematically searched. Randomized controlled trials (RCTs) assessing the effect of metformin versus placebo on cardiac function of patients with STEMI were included. Two investigators independently searched articles, extracted data, and assessed the quality of included studies. Meta-analysis was performed using the random-effect model. *Results:* Four RCTs involving 1366 patients were included in the meta-analysis. Overall, compared with control intervention in non-diabetic patients with STEMI, metformin treatment was found to significantly reduce LVEF (MD = -1.70; 95% CI = -1.71 to -1.69; P<0.00001), and increase LVEDV (MD = 0.50; 95% CI = 0.43 to 0.57; P<0.00001) and LVESV (MD = 3.80; 95% CI = 3.74 to 3.86; P<0.00001), but demonstrated no influence on NT-proBNP (MD = -1.90; 95% CI = -35.90 to 32.10; P = 0.91), creatinine (MD = -0.23; 95% CI = -2.09 to 1.62; P = 0.81), and HbA1c (MD = 0.00; 95% CI = -0.05 to 0.05; P = 1.00). *Conclusions:* Compared to control intervention non-diabetic patients with STEMI, metformin treatment significantly reduced LVEF, and improved LVEDV as well as LVESV, but had no influence on NT-proBNP, creatinine and HbA1c.

**Keywords:** Metformin, cardiac function, ST-elevation myocardial infarction, systematic review, meta-analysis

## Introduction

Cardiac dysfunction is commonly caused by acute myocardial infarction, and up to 40% of patients suffer from diastolic dysfunction which serves as an important and independent predictor of adverse outcome regardless of systolic dysfunction [1-3]. Diastolic dysfunction after myocardial infarction is associated with diabetes, the extent of myocardial injury, delayed and unsuccessful reperfusion, hypertension and female sex [4, 5]. Acute myocardial injury is reported to directly affect regional diastolic dysfunction, and subsequent infarct healing and remodeling have important association with global diastolic function [6-9]. However, there still lack effective therapies to treat or prevent the occurrence of diastolic dysfunction following myocardial infarction [10, 11].

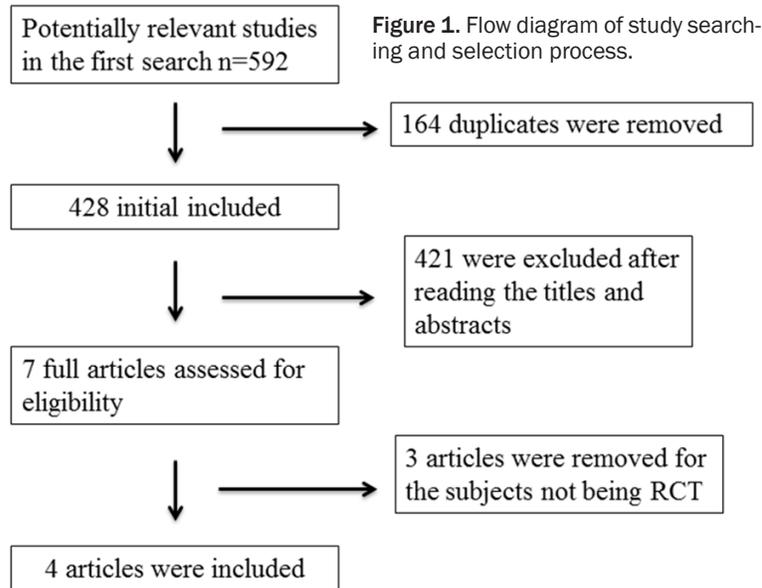
Metformin is known as the most commonly used anti-hyperglycemic agent for type 2 diabe-

tes [12-14]. Metformin has been reported to improve outcome independently of glycemic control in patient with diabetics, and may have direct cardioprotective effects [15-17]. Diastolic function in diabetes is improved by metformin treatment after coronary angiography [18]. Left ventricular end-diastolic pressure is lowered in a non-diabetic rat model [19]. However, in ST-elevation myocardial infarction (STEMI) and non-diabetic patients, metformin treatment cannot help preserve left ventricular ejection fraction (LVEF) at 4 months [20]. Considering these inconsistent effects, we therefore conduct a systematic review and meta-analysis of RCTs to evaluate the effectiveness of metformin treatment on cardiac function in patients with STEMI.

## Materials and methods

This systematic review and meta-analysis was conducted according to the guidance of the

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Preferred Reporting Items for Systematic Reviews and Meta-analysis statement [21] and the *Cochrane Handbook for Systematic Reviews of Interventions* [22]. All analyses were based on previously published studies, and thus no ethical approval and patient consent were required.

### *Literature search and selection criteria*

PubMed, EMBASE, Web of Science, EBSCO, and the Cochrane Library were systematically searched from inception to November 2017, with the following keywords: metformin, and myocardial infarction or cardiac infarction. To include additional eligible studies, the reference lists of retrieved studies and relevant reviews were also hand-searched and the process above was performed repeatedly until no further article was identified.

The inclusion criteria were as follows: (1) study population are non-diabetic patients with STEMI; (2) intervention treatments are metformin versus placebo; (3) and study design is RCT. The exclusion criteria included known diabetes, previous myocardial infarction, and severe renal dysfunction.

### *Data extraction and outcome measures*

The following information was extracted for the included RCTs: first author, publication year, sample size, baseline characteristics of patients,

metformin, control, study design. The author would be contacted to acquire the data when necessary.

The primary outcome was left ventricular ejection fraction (LVEF). Secondary outcomes include left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), N-terminal pro-brain natriuretic peptide (NT-proBNP), creatinine and glycosylated hemoglobin (HbA1c).

### *Quality assessment in individual studies*

The Jadad Scale was used to evaluate the methodological quality of each RCT included in this meta-analysis [23]. This scale consisted of three evaluation elements: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). One point would be allocated to each element if they had been mentioned in article, and another one point would be given if the methods of randomization and/or blinding had been detailedly and appropriately described. If the methods of randomization and/or blinding were inappropriate, or dropouts and withdrawals had not been recorded, then one point was deducted. The score of Jadad Scale varied from 0 to 5 points. An article with Jadad score  $\leq 2$  was considered to be of low quality. If the Jadad score  $\geq 3$ , the study was thought to be of high quality [24].

### *Statistical analysis*

Mean differences (MDs) with 95% confidence intervals (CIs) for continuous outcomes (LVEF, LVEDV, LVESV, NT-proBNP, creatinine and HbA1c) were used to estimate the pooled effects. All meta-analyses were performed using the random-effect models with DerSimonian and Laird weights. Heterogeneity was tested using the Cochran Q statistic ( $p < 0.1$ ) and quantified with the  $I^2$  statistic, which described the variation of effect size that was attributable to heterogeneity across studies. An  $I^2$  value greater than 50% indicated significant heterogeneity. Sensitivity analysis was performed to detect the influence of a single study on the overall

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**Table 1.** Characteristics of included studies

NO.	Author	Metformin group					Control group					Jada scores
		Number	Age (years)	Female (n)	BMI (kg/m <sup>2</sup> )	Methods	Number	Age (years)	Female (n)	BMI (kg/m <sup>2</sup> )	Methods	
1	Eppinga 2016	185	58.80 ± 11.82	46	27.0 ± 3.8	Metformin (500 mg bid) during 4 months after PCI for STEMI	186	58.72 ± 11.44	48	27.0 ± 3.9	Matched placebo	4
2	Al Ali 2016	118	57.9 ± 11.4	23	26.7 ± 3.7	Metformin 500 mg twice daily directly after PCI for STEMI	119	58.2 ± 10.7	30	26.9 ± 3.3	Matched placebo	4
3	Posma 2015	191	58.7 ± 11.8	47	26.9 ± 3.8	Metformin 500 mg twice daily after PCI for STEMI	188	58.8 ± 11.5	48	27.0 ± 3.9	Matched placebo	3
4	Lexis 2014	191	58.7 ± 11.8	47	26.9 ± 3.8	Metformin (500 mg) twice daily for 4 months after primary PCI for STEMI	188	58.8 ± 11.5	48	27.0 ± 3.9	Matched placebo	5

BMI: body mass index; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

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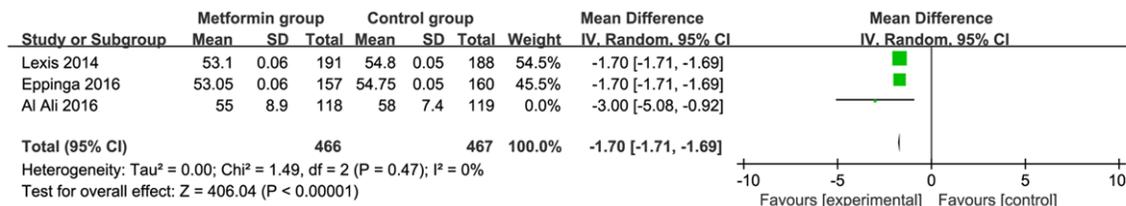


Figure 2. Forest plot for the meta-analysis of LVEF (%).

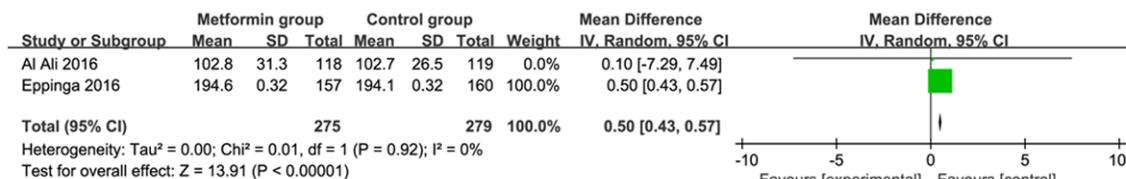


Figure 3. Forest plot for the meta-analysis of LVEDV (ml).

estimate via omitting one study in turn when necessary. Owing to the limited number (<10) of included studies, publication bias was not assessed. P<0.05 in two-tailed tests was considered statistically significant. All statistical analyses were performed with Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

### Results

#### Literature search, study characteristics and quality assessment

The flow chart for the selection process and detailed identification was presented in **Figure 1**. A total of 592 publications were identified through the initial search of databases. Ultimately, four RCTs were included in the meta-analysis [20, 25-27].

The baseline characteristics of the four eligible RCTs in the meta-analysis are summarized in **Table 1**. The four studies were published between 2014 and 2016, and sample sizes ranged from 237 to 379 with a total of 1366. There were similar baseline characteristics between metformin group and control group. Metformin 500 mg twice daily or matched placebo were taken directly after percutaneous coronary intervention (PCI) in patients with STEMI.

Among the four RCTs, three studies reported the LVEF [20, 25, 26], two studies reported the LVEDV and LVESV [25, 26], two studies reported the NT-proBNP, creatinine and HbA1c [20,

25]. Jadad scores of the four included studies varied from 3 to 5, and all four studies were considered to be high-quality ones according to quality assessment.

#### Primary outcome: LVEF

This outcome data was analyzed with the random-effect model, and the pooled estimate of the three included RCTs suggested that compared to control group in patients with STEMI, metformin intervention was associated with a significantly decreased LVEF (MD = -1.70; 95% CI = -1.71 to -1.69; P<0.00001), with no heterogeneity among the studies (I<sup>2</sup> = 0%, heterogeneity P = 0.47) (**Figure 2**).

#### Sensitivity analysis

No heterogeneity was observed among the included studies for the LVEF. Thus, we did not perform sensitivity analysis by omitting one study in each turn to detect the source of heterogeneity.

#### Secondary outcomes

Compared with control intervention in patients with STEMI, metformin intervention significantly improved LVEDV (MD = 0.50; 95% CI = 0.43 to 0.57; P<0.00001; **Figure 3**), LVESV (MD = 3.80; 95% CI = 3.74 to 3.86; P<0.00001; **Figure 4**), but had no remarkable influence on NT-proBNP (MD = -1.90; 95% CI = -35.90 to 32.10; P = 0.91; **Figure 5**), creatinine (MD = -0.23; 95% CI = -2.09 to 1.62; P = 0.81; **Figure**

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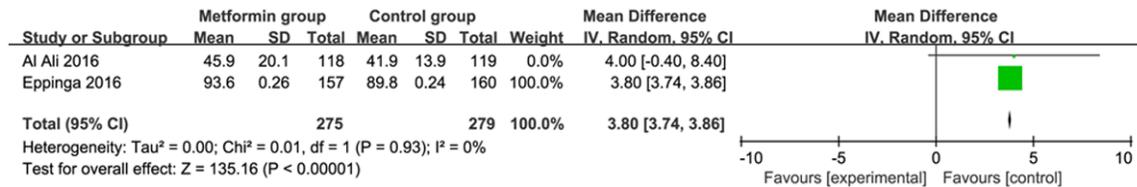


Figure 4. Forest plot for the meta-analysis of LVESV (ml).

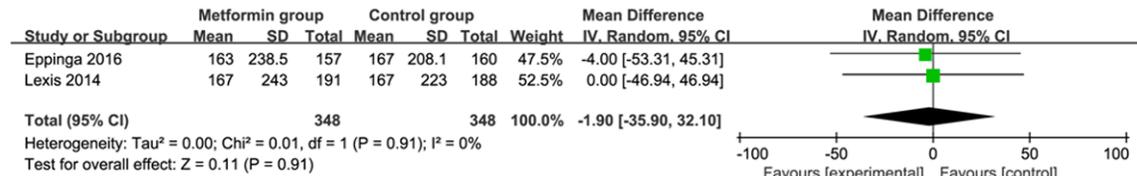


Figure 5. Forest plot for the meta-analysis of NT-proBNP (ng/L).

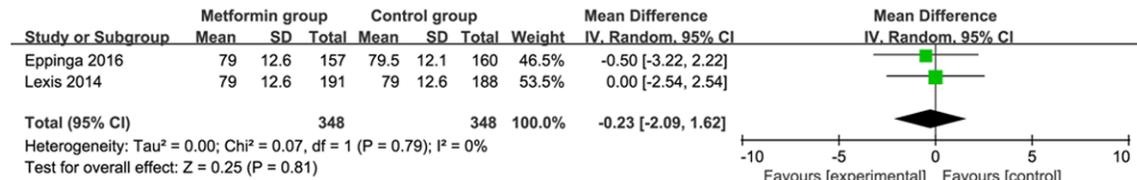


Figure 6. Forest plot for the meta-analysis of creatinine (µmol/L).

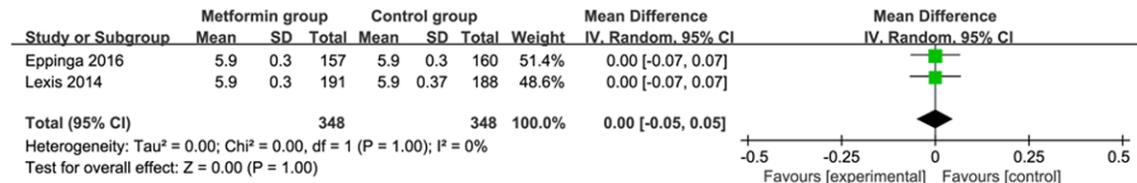


Figure 7. Forest plot for the meta-analysis of HbA1c (%).

6), and HbA1c (MD = 0.00; 95% CI = -0.05 to 0.05; P = 1.00; Figure 7).

## Discussion

It is well known that left ventricular function is thought to be the most important predictor of morbidity and mortality after STEMI. One clinical study reports that 500 mg of metformin twice daily for 4 months shows no notable influence on LVEF in patients without diabetes after primary PCI for STEMI [20]. Concentration of NT-proBNP has the strong relationship with LVEF and clinical outcome [28, 29]. In our meta-analysis, compared to control intervention in patients with STEMI, metformin as adjunct to optimal medical treatment is associated with

significantly reduced LVEF, and improved LVE-DV and LVESV, with no remarkable effect on NT-proBNP. To our knowledge, this meta-analysis is the first to study the effects of metformin on cardiac function in non-diabetic patients with STEMI.

However, these results are not consistent with experimental studies. Metformin has been found to result in the reduced infarct size of 22% and relative improvement in LVEF of 52% in a non-diabetic rat model of myocardial infarction [19]. In a mouse model, administration of metformin is effective in improving left ventricular function during ischemia-reperfusion [30]. There may be several reasons for the lack of efficacy of metformin on LVEF in STEMI. Earlier

animal studies reports the protective effects of metformin are mainly performed in animals undergoing occlusion of the left main or the proximal left anterior descending coronary artery [30, 31]. This meta-analysis only includes patients presenting with acute myocardial infarction and excludes the patients with diabetes. The exclusion of this high-risk category may affect our findings and is contrast with commonly real-life practice [32].

In addition, the lack of efficacy of metformin may be due to the insufficient time window between coronary occlusion and achieving effective plasma levels of metformin. On average, the time between PCI and the achievement of effective plasma levels of metformin is approximately 4 hours [33]. Effective plasma metformin levels during reperfusion or earlier may be very important for the clinical outcomes of STEMI. In one recent RCT of metabolic syndrome patients, metformin treatment (250 mg 3 times daily) starting 7 days prior to elective PCI is revealed to produce a smaller cardiac biomarker release and a favorable 1-year clinical outcome [34]. The beneficial effects of metformin on left ventricular function and myocardial infarct size are proven when metformin is administered prior to or during ischemia-reperfusion in experimental animal studies [30].

Furthermore, the dose of metformin administration (500 mg twice daily) may be insufficient for the efficacy in myocardial infarction patients and is generally well-tolerated, but the highest possible dose of metformin may cause lactic acidosis or impaired renal function [35]. Long-term metformin treatment results in lower peak levels of biochemical markers of myocardial infarct size and improved outcome compared with other glucose-lowering therapies in patients with diabetes [17, 36]. Metformin treatment (500 mg twice daily) for 4 months is reported to have no significant effect on glycemic control compared to placebo, as evidenced by the analysis of glucose and HbA1c levels [20]. Our meta-analysis indicates that metformin treatment (500 mg twice daily) demonstrates no notable influence on creatinine, and HbA1c in STEMI. However, in patients with coronary artery disease but without diabetes, metformin treatment (850 mg twice daily for 18 months) lead to a significantly reduced HbA1c values [37]. More higher doses and longer duration of metformin treatment may have the benefits to clinical outcome for STEMI.

Several limitations should be taken into account. Firstly, our analysis is based on only four RCTs, and more clinical trials with large sample are needed to explore this issue. The doses and duration of metformin treatment in this meta-analysis may be insufficient for the efficacy of metformin treatment. Next, future meta-analysis should perform subgroup analysis based on non-diabetic patients with myocardial infarction and diabetic patients with myocardial infarction. Finally, some unpublished and missing data may lead bias to the pooled effect.

Metformin treatment may show no benefits to cardiac function in patients with non-diabetic patients with STEMI, but more studies should be performed to investigate the higher dose and longer duration of metformin in STEMI.

### Disclosure of conflict of interest

None.

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