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SYSTEMATIC REVIEW AND META-ANALYSIS

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Efficacy of Adenosine in Patients With Acute Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

A PRISMA-Compliant Meta-Analysis

Qijun Gao, MD, Bo Yang, MD, Yi Guo, MD, and Feng Zheng, MD

Abstract: Whether adenosine offers cardioprotective effects when used as an adjunctive therapy for patients with acute myocardial infarction (AMI) undergoing primary percutaneous coronary intervention (PCI) remains controversial.

To evaluate, via meta-analysis, the efficacy of adenosine in patients with AMI undergoing PCI.

Randomized controlled trials (RCTs) published in Medline, Embase, and the Cochrane Central Register of Controlled Trials.

RCTs of patients with AMI undergoing primary PCI, comparing adenosine treatment and placebo groups and reporting mortality, thrombolysis in myocardial infarction (TIMI) flow grade, myocardial blush grade (MBG), re-infarction, left-ventricular ejection fraction (LVEF), ST-segment elevation resolution (STR), recurrent angina, or heart failure (HF).

Risk of bias was assessed by the Cochrane guidelines and publication bias by Egger's test. For studies reported in multiple publications, the most complete publication was used. Arms using different dosing schedules were merged. Mean differences (MDs) or risk ratios (RRs) were determined.

Data were extracted from 15 RCTs involving 1736 patients. Compared with placebo, adenosine therapy was associated with fewer occurrences of heart failure (RR: 0.65, 95% confidence interval [CI]: 0.43-0.97, $P = 0.03$) and no-reflow (TIMI flow grade <3, RR: 0.62, 95% CI: 0.45-0.85, $P = 0.003$; MBG 0-1, RR: 0.81; 95% CI: 0.67-0.98, $P = 0.03$), more occurrences of STR (RR: 1.19, 95% CI: 1.07-1.31, $P < 0.00001$), but no overall improvement of LVEF (MD: 2.29, 95% CI: −0.09 to 4.67, $P = 0.06$). Adenosine improved LVEF in the intravenous subgroup and the regular-dose intracoronary (IC) subgroup (0.24-2.25 mg) compared with placebo (MD: 2.68, 95% CI: 0.66-4.70, $P = 0.009$). Adenosine was associated with a poorer LVEF in the high-dose (4-6 mg) IC subgroup (MD: −2.40; 95% CI: −4.72 to −0.09, $P = 0.04$). There was no significant evidence that adenosine reduced rates of all-cause mortality, cardiovascular mortality or re-infarction after PCI.

Adenosine dosage and administration routes, baseline profiles, and endpoints differed among included RCTs. Performance, publication, and reporting biases remain possible.

Adenosine therapy appears to improve several outcomes in patients with AMI after PCI, but there is no evidence that adenosine can reduce mortality rates.

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Abbreviations: AE = adverse event, AMI = acute myocardial infarction, CI = confidence interval, HF = heart failure, LVEF = left-ventricular ejection fraction, MACE = major adverse cardiovascular event, MBG = myocardial blush grade, MD = mean difference, PCI = percutaneous coronary intervention, RCT = randomized control trial, RR = risk ratio, STEMI = ST-segment elevation myocardial infarction, STR = ST-segment resolution, TIMI = thrombolysis in myocardial infarction.

INTRODUCTION

According to the World Health Organization, more people die from cardiovascular disorders each year than from any other cause worldwide. The Global Burden of Disease study classified ischemic heart disease as the leading cause of global mortality, accounting for 1.4 and 5.7 million deaths in developed and developing regions, respectively.[1] Each year, more than 3.0 million people experience acute ST-elevation myocardial infarction (STEMI). The first choice of treatment for STEMI is primary percutaneous coronary intervention (PCI).[2] Although PCI is successful in most cases, up to 40% of patients do not achieve complete myocardial reperfusion despite successful treatment of the culprit lesion. This phenomenon is defined as ''no-reflow.''[3] Acute myocardial infarction (AMI) with no-reflow after primary PCI is difficult to treat and strongly associated with poor in-hospital and long-term outcomes.

In experimental animals, adenosine reduces ischemia/reperfusion injury, limits infarct size, and improves ventricular function.[4] However, studies with adenosine in patients with AMI undergoing PCI have yielded controversial results. For example, 2 meta-analyses failed to draw definitive conclusions on clinical outcomes.[5,6] Therefore, we performed a meta-analysis to reevaluate the efficacy of adenosine in patients with AMI undergoing PCI.

METHODS

The present meta-analysis was performed in accordance with established methods laid out in the Cochrane guidelines[7]

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and in compliance with the PRISMA[8] statement for reporting systematic reviews and meta-analyses in healthcare interventions. The study was approved by the Ethics Committee of Renmin Hospital of Wuhan University.

Literature Search

Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for randomized controlled trials (RCTs) published between January 1995 and December 2014, no language restrictions were considered. The following search terms were used: adenosine, ST-elevation myocardial infarction, AMI, and/or PCI.

Study Selection and Inclusion Criteria

Two reviewers performed study selection independently, with any disagreements resolved through discussion and with the aid of a third reviewer, if necessary. Studies were considered potentially eligible for the meta-analysis if they met the following criteria: CTs involving patients with AMI undergoing primary PCI, comparing an adenosine treatment group with a placebo group, and reporting at least one of the following outcomes: mortality, thrombolysis in myocardial infarction (TIMI) flow grade, myocardial blush grade (MBG), re-infarction, left-ventricular ejection fraction (LVEF), ST-segment elevation resolution (STR), or heart failure (HF). Trials were excluded if they were abstracts, letters, and reviews.

Data Extraction and Quality Assessment

Two reviewers independently undertook the data extraction and quality assessment procedures. Disagreements were resolved through discussion, aided by the opinion of a third reviewer if necessary. The following information was extracted from the studies: author, year, design, duration, sample size, study patient population, clinical outcomes, angiographic outcomes, cardiac imaging-related outcomes, and STR. If the report of a study did not contain all of the details required, then an email was sent to the authors to ask for the missing information. For studies reported in multiple publications, data were extracted from the most complete publication, with the other publications serving as supplements. In trials with more than 2 arms, arms using different dosing schedules were merged to avoid duplicating the control arm. Risk of bias was assessed in accordance with guidelines in the Cochrane Handbook. Publication bias was tested by the Egger's test.

Statistical Analyses

For continuous data, mean differences (MDs) and the corresponding 95% confidence intervals (CIs) were analyzed. For dichotomous data, risk ratios (RRs) were analyzed. Study heterogeneity was assessed for each outcome. Homogenous outcomes were analyzed by fixed-effects models. For heterogeneous outcomes, clinical heterogeneity across studies was assessed and, if present, addressed by sensitivity or subgroup analyses. If significant heterogeneity remained, then a random-effects model or descriptive analyses were used, as appropriate. Statistical analyses were performed by using relevant software (RevMan 5.2 or STATA12.0, for Egger's test). A 2-sided P value <0.05 was considered statistically significant.

RESULTS

Literature Search

Of the 2403 articles identified (Embase/Medline 2188 and CENTRAL 215), 252 articles were potentially relevant. After screening the titles and abstracts of these articles, 218 studies were excluded. The remaining 34 studies were retrieved for a more detailed evaluation. Nineteen studies were excluded because they had no control group (3 studies),[9–11] had different study populations (12 studies),[12–23] were duplicate publications of the same study population (3 studies),[19,24–25] or were not RCTs (1 study).[26] Thus, 15 clinical trials were included in the final analysis[27–41] (Figure 1).

Endpoints

Table 1 lists the endpoints used in each study.[27–41] Angiographic outcomes (TIMI flow grade and MBG) were measured at the end of balloon dilation or after PCI with stenting. The cardiac imaging-related outcome (LVEF) was assessed by echocardiography or magnetic resonance imaging at different time intervals. We tried to pool the data for LVEF and HF assessed 1 month to 1 year after PCI; however, 2 papers that evaluated LVEF and 2 papers that evaluated HF only provided these data at 2 weeks after PCI. Ten studies reported STR, which was defined as the resolution of ST-segment elevation $\geq$70% (8 studies) or $\geq$50% (2 studies).

Study and Patient Characteristics

Trials included in this meta-analysis comprised 1736 patients (control group, n = 858; adenosine group, n = 878). All 15 trials compared between a placebo arm and an adenosine arm. Adenosine was administered by an intravenous (IV) protocol (3 studies) or by an intracoronary (IC) protocol (12 studies), including boluses or continuous infusion. Results of the meta-analyses are shown in Figures 2–12. Baseline characteristics of individual trials are given in Table 1.

Quality Assessment of Included Trials

All of the included studies were RCTs. Although they did not describe the method of randomization or allocation concealment, the outcomes were assessed by researchers who were blinded to the results or independent of the study. The overall

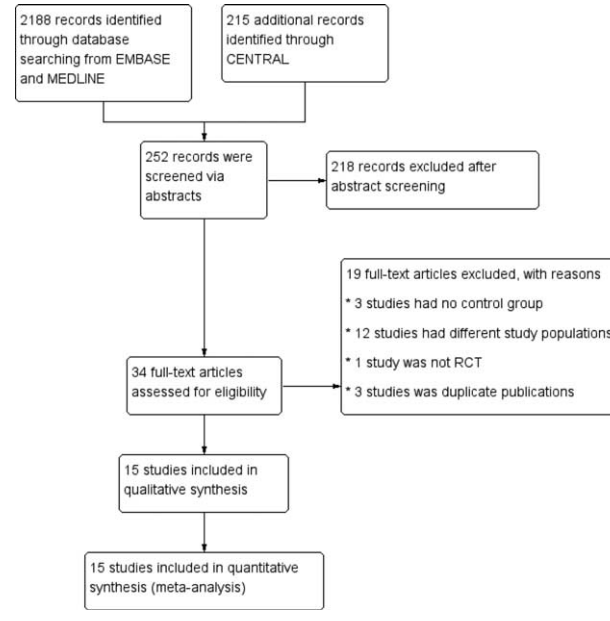

FIGURE 1. Flow chart of the meta-analysis.

TABLE 1. Summary of Randomized Studies Comparing Adenosine Versus Placebo

Trial	No. of Cases/ Controls	Follow-Up, mo	Route	Dose	Endpoints	STR %
Marzilli et al[34]	27/27	In hospital	IC	4 mg in 1 min	HF, mortality, no-reflow, re-infarction	NA
Stoel et al[36]	27/22	12	IC	60 mg in 5–10 min	HF, mortality, STR	70
Fokkema et al[31]	226/222	1	IC	120 μg twice	AE, mortality, re-infarction, STR, no-reflow	70
Desmet et al[30]	56/54	4	IC	4 mg bonus	Mortality, LVEF, no-reflow, STR	70
Grygier et al[38]	35/35	12	IC	1 mg RCA, 2 mg LCA twice	MACE, LVEF, no-reflow, STR	70
Wang et al[40]	35/34	1	IV	50 μg/kg/min for 3 h	HF, LVEF, mortality, re-infarction	NA
Tong et al[37]	130/128	12	IC	2 mg in 1 min twice	MACE, no-reflow, STR	70
Petronio et al[37]	30/30	6	IC	4 mg in 1 min	Mortality, LVEF, no-reflow, STR	50
Micari et al[32]	14/16	1	IV	50–70 μg/kg/min for 3 h	AE, LVEF, mortality	NA
Niccoli et al[29]	80/80	1	IC	120 μg bolus + 2 mg over 2 min	AE, MACE, no-reflow, STR	70
Garcia-Dorado et al[28]	100/97	6	IC	2.25 mg/min for 2 min	LVEF, mortality, no-reflow	70
Ji et al[27]	23/27	1	IC	300 μg	AE, LVEF, TIMI	NA
Akturk et al[33]	16/15	6	IC	240 μg	LVEF, mortality, STR, TIMI	50
Zhang et al[41]	32/31	1	IV	50–70 μg/kg/min for 3 h	HF, LVEF, mortality, no-reflow, re-infarction	NA
Darahim et al[39]	20/40	In hospital	IC	6 mg bonus	LVEF, mortality, no-reflow, re-infarction, STR	70

AE = adverse event; HF = heart failure; IC = intracoronary; IV = intravenous; LCA = left coronary artery; LVEF = left-ventricular ejection fraction; MACE = major adverse cardiovascular event; NA = not available; RCA = right coronary artery; STR = ST-segment elevation resolution; TIMI = thrombolysis in myocardial infarction.

risk of bias of the included studies was moderate (Figure 13). There was no evidence of publication bias, according to the nonsignificant results of the Egger's test for TIMI flow grade, HF, LVEF, or STR (Figure 14).

OUTCOMES

Mortality Rates

Among 14 studies reporting data on all-cause mortality for 1686 participants, a fixed-effects model revealed no evidence of a reduction in all-cause mortality with adenosine compared with placebo (RR: 0.73, 95% CI: 0.42–1.28, $P = ï0.27$, $I^2 = 0\%$; Figure 2). Seven studies reported data on cardiovascular mortality for 621 participants. There was no evidence of a reduction in cardiovascular mortality with adenosine compared with placebo, according to a fixed-effects model (RR: 0.52, 95% CI: 0.23–1.16, $P = ï0.11$, $I^2 = 0\%$; Figure 3).

HF and LVEF

Seven trials reported data on HF at 1 week to 1 year after PCI for 750 participants. According to the results of a fixed-

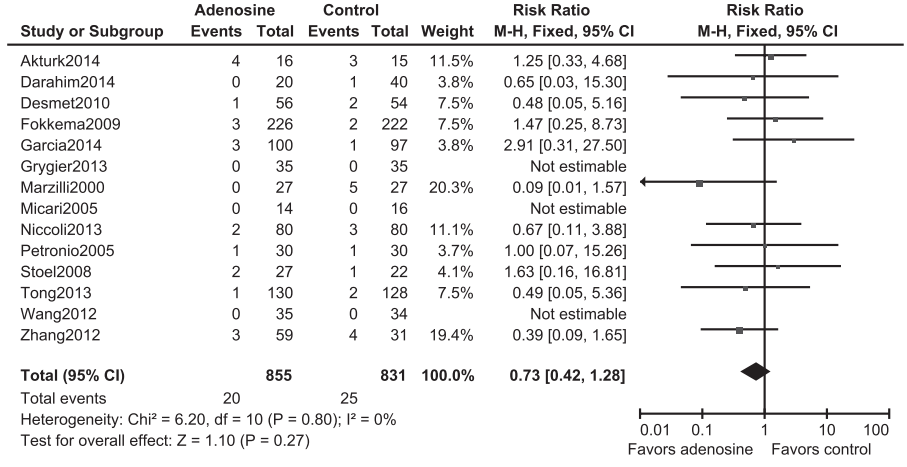

FIGURE 2. Forest plot of adenosine versus placebo for all-cause mortality. Overall and individual risk ratios and 95% confidence intervals are reported.

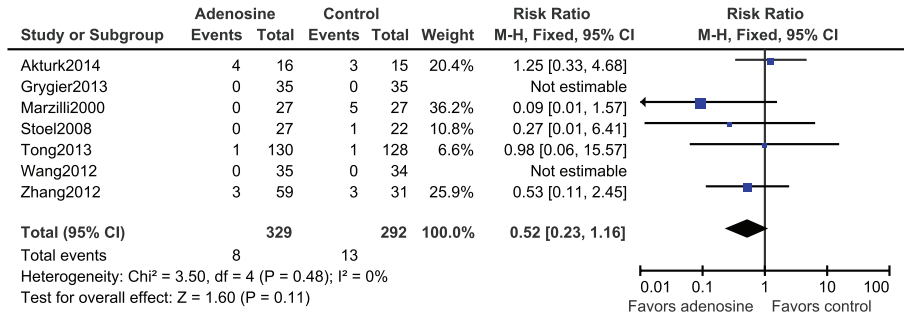

FIGURE 3. Forest plot of adenosine versus placebo for cardiovascular mortality. Overall and individual risk ratios and 95% confidence intervals are reported.

effects model, there was a significant reduction in the incidence of HF with adenosine compared with placebo (RR: 0.65, 95% CI: 0.43–0.97, $P = 0.03$, $I^2 = 45.1\%$; Figure 4). Ten trials with 678 participants reported data on LVEF at 1 week to 1 year after PCI. Compared with placebo, adenosine did not significantly improve LVEF according to a random-effects model (MD: 2.29, 95% CI: −0.09 to 4.67, $P = 0.06$, $I^2 = 76\%$; Figure 5).

No-Reflow and Myocardial Reperfusion

Adenosine should be administered before reperfusion to improve the coronary TIMI flow. One study in which adenosine was administered after PCI was excluded to reduce heterogeneity. Eleven trials with 1556 participants reported data on TIMI flow grade <3. According to the results of a fixed-effects model, compared with placebo, adenosine administered before reperfusion reduced the incidence of TIMI flow grade <3 after PCI (RR: 0.62, 95% CI: 0.45–0.85, $P = 0.003$, $I^2 = 29\%$; Figure 6). Six trials with 1108 participants reported data on MBG after PCI. According to the results of a fixed-effects model, compared with placebo, adenosine reduced the incidence of MBG = 0 to 1 after PCI (RR: 0.81, 95% CI: 0.67–0.98, $P = 0.03$, $I^2 = 36\%$; Figure 7). Ten trials with 1361 participants reported STR. An incidence of STR ≥50% or 70% after PCI was observed more frequently in the adenosine group than in the control group, according to the results of a fixed-effects model (RR:1.21, 95% CI: 1.10–1.32, $P < 0.00001$, $I^2 = 36\%$; Figure 8).

Re-Infarction

Six studies assessed re-infarction in 1138 participants. According to fixed-effects models, there was no evidence of a reduction in re-infarction (RR: 0.83, 95% CI: 0.38–1.82, $P = 0.64$, $I^2 = 0\%$) with adenosine at short-term follow-up (Figure 9).

Adverse Events (AEs)

Five RCTs with 648 people reported data on bradycardia, 3 RCTs with 578 people reported data on hypotension, and 8 RCTs with 1232 participants reported data on atrioventricular (AV) block. Compared with placebo, adenosine was not associated with a higher incidence of hypotension (RR: 2.79, 95% CI: 0.76–10.25, $P = 0.12$, $I^2 = 71\%$), according to a random-effects model (Figure 10). However, there was a greater likelihood of AV block (fixed-effect model—RR: 6.45, 95% CI: 3.77–11.06, $P < 0.00001$, $I^2 = 0\%$; Figure 11) or bradycardia (random-effect model—RR: 3.47, 95% CI: 1.03–11.71, $P = 0.05$, $I^2 = 66\%$; Figure 12) in the adenosine group compared with the placebo group.

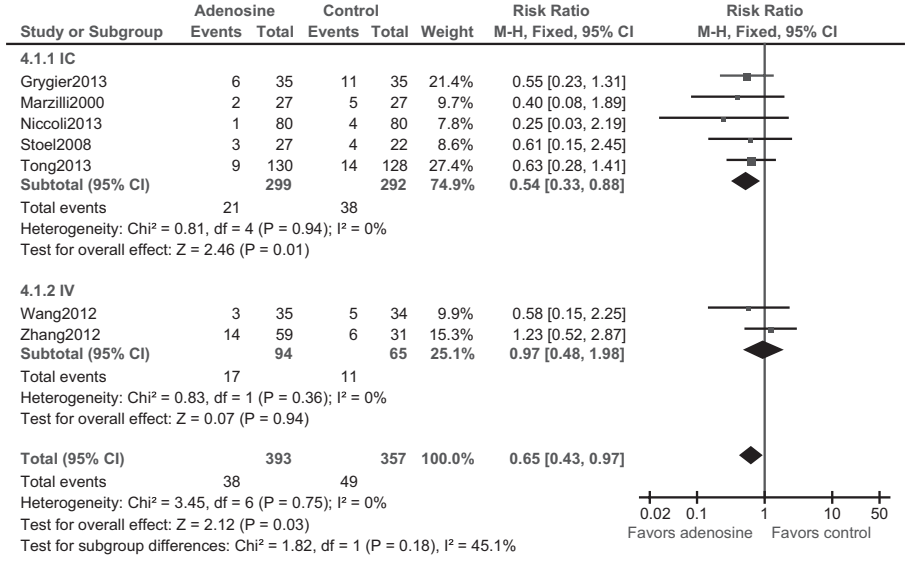

FIGURE 4. Forest plot of adenosine versus placebo for heart failure. Overall and individual risk ratios and 95% confidence intervals are reported.

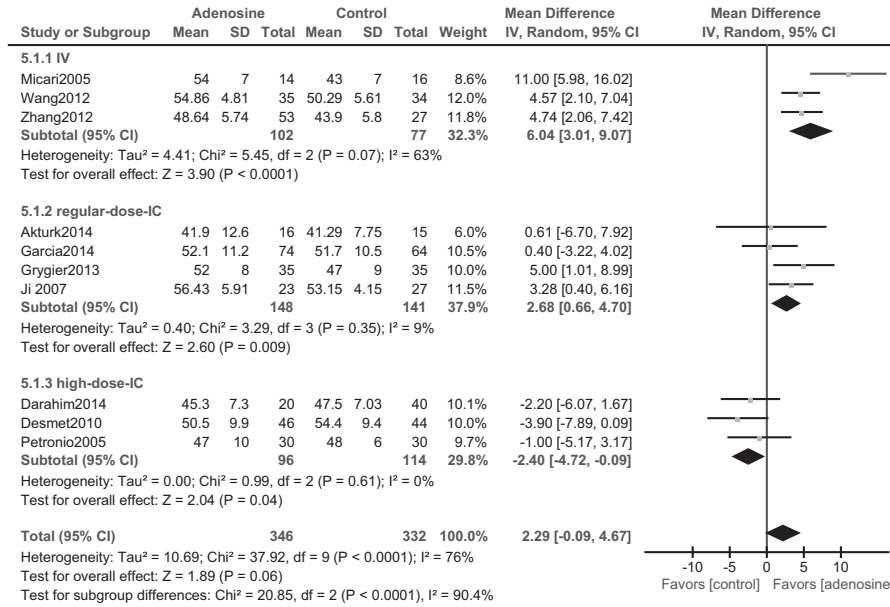

FIGURE 5. Forest plot of adenosine versus placebo for left-ventricular ejection fraction at 1 week to 12 months after percutaneous coronary intervention. Overall and individual risk ratios and 95% confidence intervals are reported.

Subgroup and Sensitivity Analyses

We performed subgroup analyses to assess the effects of IC versus IV adenosine for the outcomes of LVEF and HF, and regular-dose (IC bolus of 0.24–2.25 mg) versus high-dose adenosine (IC bolus of 4–6 mg) for the outcome of LVEF. In all 3 trials that included an IV subgroup, IV adenosine improved the LVEF compared with placebo. IC bolus of regular-dose adenosine was associated with improved LVEF (MD: 2.68, 95% CI: 0.66–4.70, $P = ï0.009$, $I^2 = 9\%$), whereas IC bolus of high-dose adenosine was associated with a worsened LVEF (MD: −2.40; 95% CI: −4.72 to −0.09, $P = ï0.04$, $I^2 = 0\%$; Figure 5) compared with placebo. IC adenosine reduced the occurrence of HF compared with the placebo group, according to a fixed-effects model (RR: 0.54, 95% CI: 0.33–0.88, $P = ï0.01$, $I^2 = 0\%$).

Several sensitivity analyses were conducted to explore the robustness of the results, by removing each study 1 at a time. These analyses did not indicate that any single study influenced the overall results for STR or TIMI flow grade <3.

DISCUSSION

In this meta-analysis of 15 RCTs involving 1736 participants to study the impact of adenosine on patients with AMI undergoing primary PCI, adenosine treatment was not found to have any effect on mortality or re-infarction. However, because of the insufficient sample size, the meta-analysis had limited ability to study these endpoints with adequate power. On the other hand, adenosine appeared to offer potentially beneficial effects on myocardial reperfusion, the occurrence of HF and no-reflow, besides, IV and IC regular-dose adenosine improved LVEF.

Adenosine is an endogenous nucleoside found in large quantities in the myocardial and endothelial cells. It activates 4 receptors, producing physiological effects that attenuate many of the proposed mechanisms of reperfusion injury. Adenosine is a well-known adjunctive therapy for AMI.[13] Experimental models and animal studies have demonstrated that adenosine plays a protective role in reperfusion injury when administered in the perireperfusion period, and that it decreases

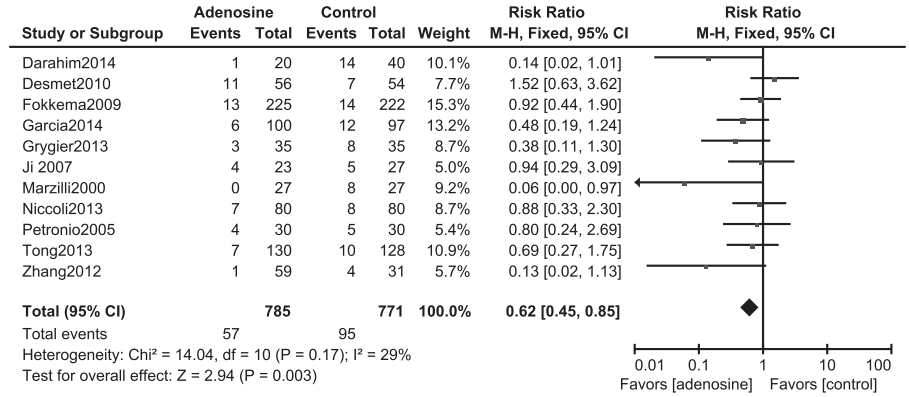

FIGURE 6. Forest plot of adenosine versus placebo for thrombosis in myocardial infarction flow grade <3. Overall and individual risk ratios and 95% confidence intervals are reported.

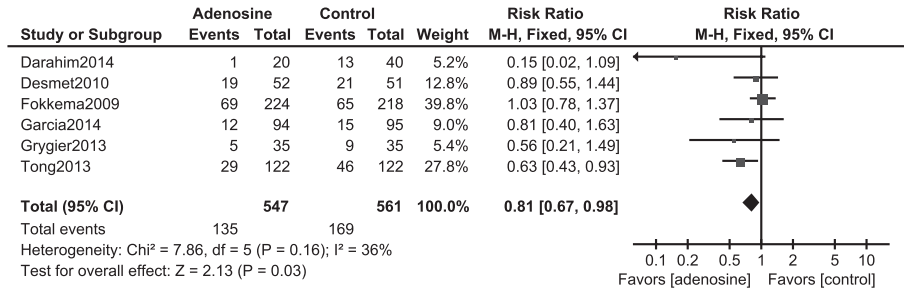

FIGURE 7. Forest plot of adenosine versus placebo for myocardial blush grade 0 to 1. Overall and individual risk ratios and 95% confidence intervals are reported.

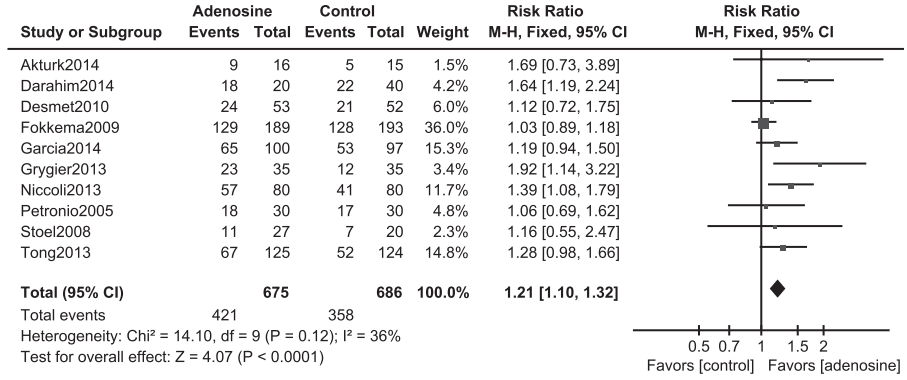

FIGURE 8. Forest plot of adenosine versus placebo for ST-segment elevation resolution. Overall and individual risk ratios and 95% confidence intervals are reported.

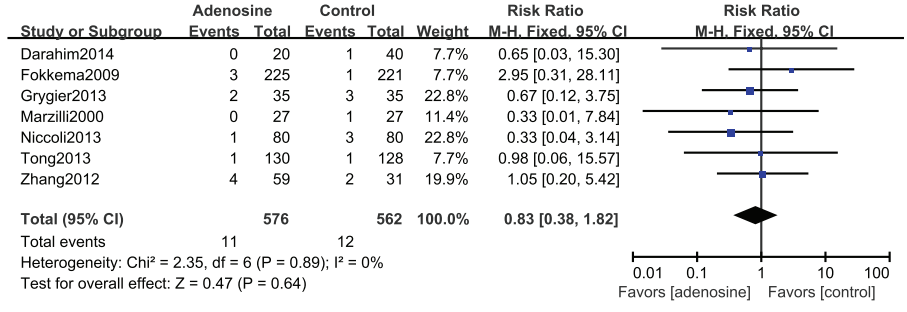

FIGURE 9. Forest plot of adenosine versus placebo for re-infarction. Overall and individual risk ratios and 95% confidence intervals are reported.

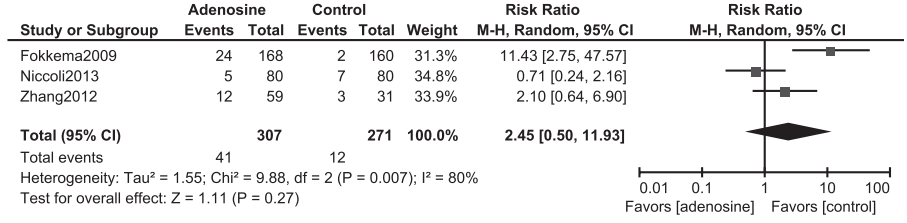

FIGURE 10. Forest plot of adenosine versus placebo for bradycardia. Overall and individual risk ratios and 95% confidence intervals are reported.

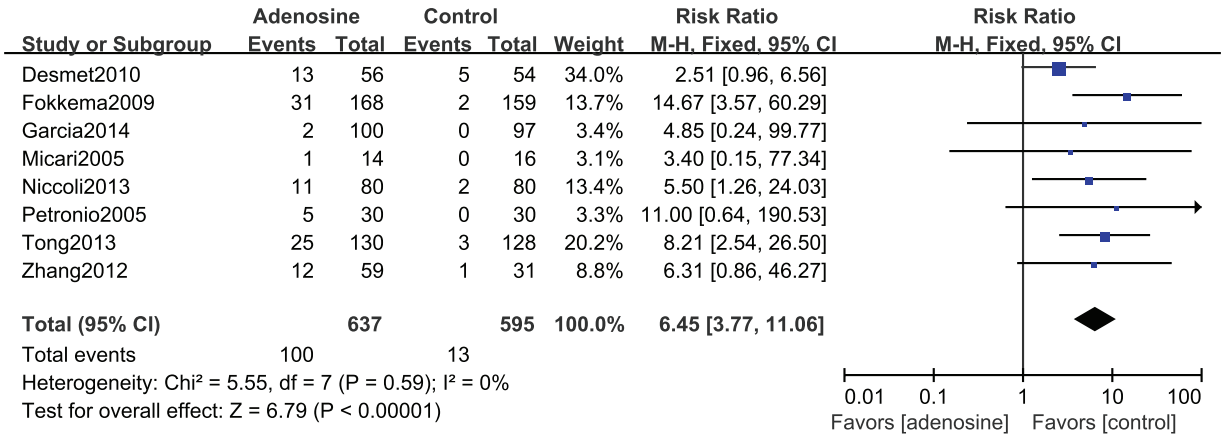

FIGURE 11. Forest plot of adenosine versus placebo for atrioventricular block. Overall and individual risk ratios and 95% confidence intervals are reported.

neutrophil-mediated mechanical obstruction of the capillary channels. Owing to its potent arteriolar vasodilator properties, adenosine can block both the release of vasoconstrictors (eg, endothelin, leukotrienes, platelet-activating factor) by activated platelets and neutrophils, as well as the effects of vasoconstrictors present in the vascular bed after reperfusion.

Adenosine markedly inhibits superoxide anion production by neutrophils and decreases the number of neutrophils in the reperfused bed.[42] Other animal studies[43] found that adenosine, via upregulation of thrombospondin-1, can increase the blood capillary density at the interface between normal and ischemic tissues after AMI. Furthermore, microRNAs participate in cardiovascular disease processes and function as potential therapeutic targets.[44,45] Adenosine has been demonstrated to regulate the production of RNAs as signaling molecules.[46] Thus, adenosine can reduce infarct size and improve cardiac function via multiple protective roles in reperfusion injury, angiogenesis, and the modulation of small RNA molecules.

Adenosine administration was associated with a lower incidence of TIMI flow grade <3 and MBG of 0 to 1, and with an increased incidence of STR after PCI. These findings indicate that adenosine was associated with better myocardial reperfusion and less incidence of no-reflow, which should theoretically lead to an improved LVEF. However, adenosine did not have accordantly beneficial effects on LVEF. In subgroup analysis, IV adenosine significantly improved LVEF compared with control in all 3 trials. In contrast, LVEF was improved in the regular-dose IC subgroup, but impaired in the high-dose IC subgroup, compared with placebo. These results suggest that the optimal dose for IC administration has yet to be ascertained.

Some reasons for the lack of consistent beneficial effects of IC adenosine in our meta-analysis may be hypothesized. First, the dose of IC adenosine administered by infusion or bolus had a wide range (0.24–60 mg). Second, when using an IC bolus, most studies gave adenosine within 1 min, which may not be sufficient to provide ideal protection. For example, oxygen-derived free radicals, which are major contributors to reperfusion damage, reach peak concentrations in the coronary vessel between 2 and 3 min after the return of oxygenated blood.[47] Finally, adenosine should be delivered immediately before or after reperfusion. However, 2 studies supplied adenosine as an IC bolus after stenting, thereby missing the most important time period to reduce reperfusion damage.

Observed AEs of adenosine included bradycardia, hypotension, dyspnea, chest pain, flushing, AV block, and, rarely, broncho spasm and headache. Adenosine was associated with a higher incidence of AV block and bradycardia compared with placebo. However, all AEs disappeared within 2 to 3 min due to the short half-life of adenosine, and no clinical sequelae were observed.

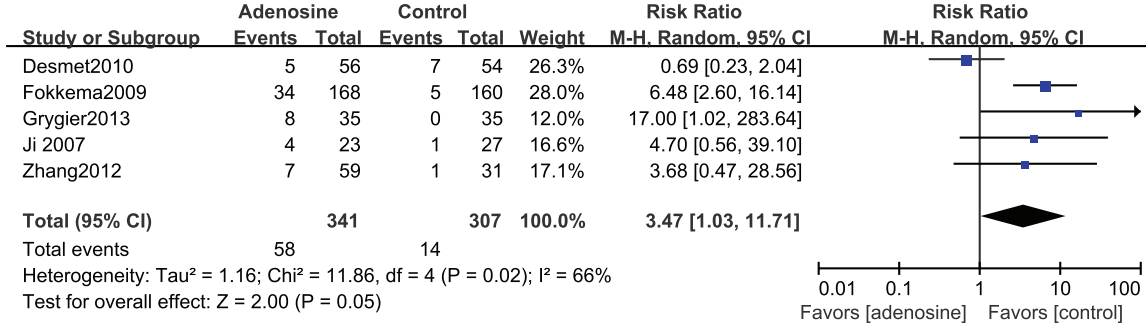

FIGURE 12. Forest plot of adenosine versus placebo for hypotension. Overall and individual risk ratios and 95% confidence intervals are reported.

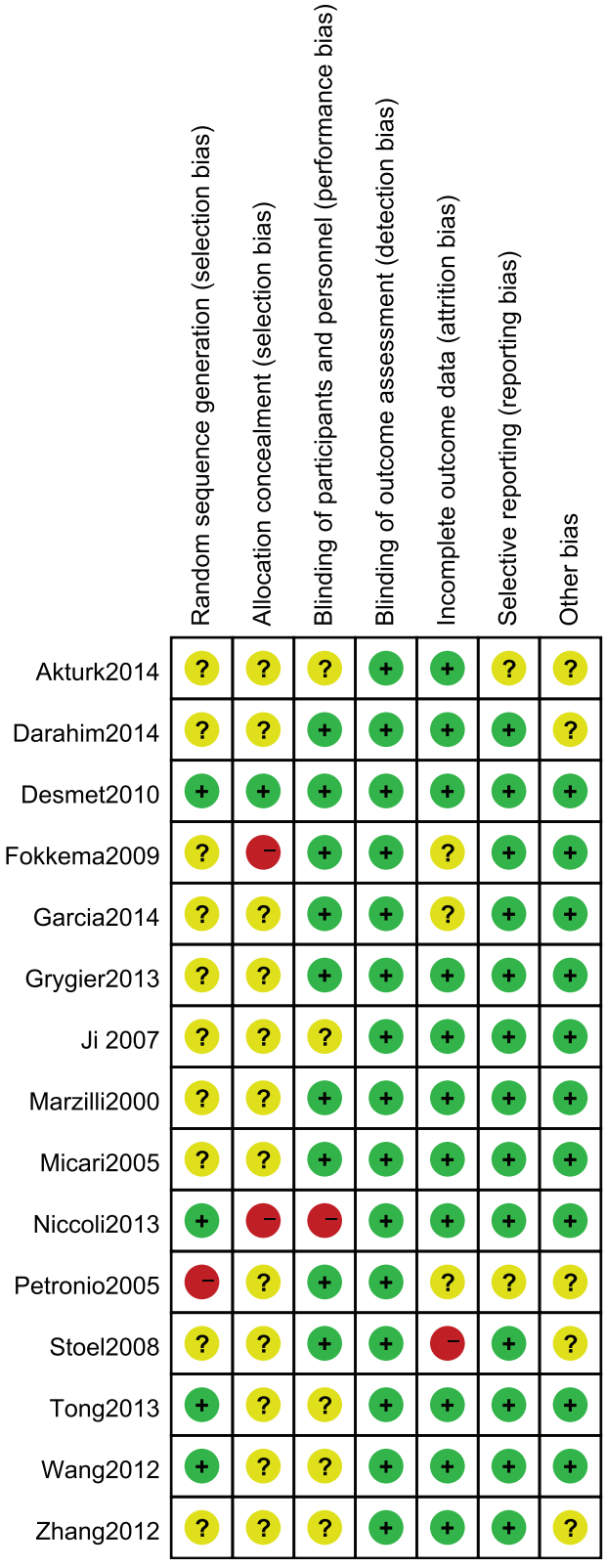

FIGURE 13. Risk of bias summary. Review of authors' judgments about each risk of bias item for each included study.

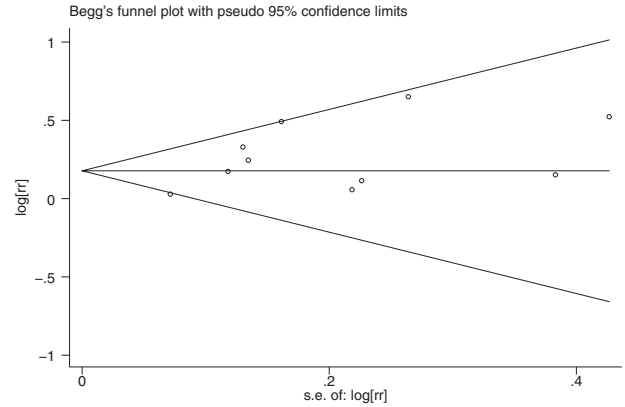

FIGURE 14. Funnel plot for meta-analysis of the incidence of ST-segment elevation resolution. The x-axis is the standard error of the log-transformed RR (logrr), and the y-axis is the logrr. The horizontal line represents the overall estimated logrr.

Three previous meta-analyses have assessed the impact of adenosine on patients with AMI undergoing primary PCI. Mukesh et al[5] analyzed 7 studies involving 1030 participants who were treated with IC adenosine. They assessed mortality, HF, major adverse cardiovascular event (MACE), STR, LVEF, TIMI flow, MBG, and side effects, but were unable to draw definitive conclusions on any of the clinical outcomes. Their meta-analysis included 2 studies that did not meet our inclusion criteria: one was not an RCT[26] and one used a nonplacebo control group.[10] Aung Naing et al[6] assessed no-reflow after primary PCI in patients with AMI treated with adenosine and verapamil. Their meta-analysis included 10 RCTs involving 947 participants, including 9 RCTs associated with adenosine and 1 with verapamil. These authors also failed to come to a definitive conclusion on any clinical outcome. Recently, Polimeni et al[48] reported a meta-analysis of conference abstracts, which included 10 RCTs in which patients were treated with IC adenosine. They found that adenosine treatment improved major cardiovascular AE and HF rates in patients with STEMI treated with PCI. Their findings are partly consistent with our conclusions.

LIMITATIONS

Our meta-analysis included studies using different dosages and administration routes of adenosine, baseline profiles, endpoints, and definitions of the endpoints. There may have been a performance bias due to an imbalance of co-interventions across the intervention and control arms. There was also a potential for publication or reporting bias. However, most of the trials had negative results, which should reduce this potential risk. In addition, Egger's tests for TIMI flow grade, HF, LVEF, and STR did not indicate any evidence of publication bias.

CONCLUSIONS

Adenosine treatment of patients with AMI undergoing primary PCI appears to be associated with a lower incidence of HF and no-reflow, improved myocardial reperfusion, and relatively better LVEF. However, because of the limitations of this study, this statement should be regarded as hypothesis-generating rather than conclusive. Adenosine did not seem to

have any effect on mortality or re-infarction, although these outcomes were limited by the fact that the sample size was insufficient for achieving adequate power. Larger randomized trials are warranted.

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