Clinical benefit of adenosine as an adjunct to reperfusion in ST-elevation myocardial infarction patients: An updated meta-analysis of randomized controlled trials

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Background: Adenosine administered as an adjunct to reperfusion can reduce coronary no-reflow and limit myocardial infarct (MI) size in ST-segment elevation myocardial infarction (STEMI) patients. Whether adjunctive adenosine therapy can improve clinical outcomes in reperfused STEMI patients is not clear and is investigated in this meta-analysis of 13 randomized controlled trials (RCTs).

Methods: We performed an up-to-date search for all RCTs investigating adenosine as an adjunct to reperfusion in STEMI patients. We calculated pooled relative risks using a fixed-effect meta-analysis assessing the impact of adjunctive adenosine therapy on major clinical endpoint including all-cause mortality, non-fatal myocardial infarction, and heart failure. Surrogate markers of reperfusion were also analyzed.

Results: 13 RCTs (4273 STEMI patients) were identified and divided into 2 subgroups: intracoronary adenosine versus control (8 RCTs) and intravenous adenosine versus control (5 RCTs). In patients administered intracoronary adenosine, the incidence of heart failure was significantly lower (risk ratio [RR] 0.44 [95% CI 0.25–0.78], P = 0.005) and the incidence of coronary no-reflow was reduced (RR for TIMI flow=3 postreperfusion 0.68 [95% CI 0.47–0.99], P = 0.04). There was no difference in heart failure incidence in the intravenous adenosine group but most RCTs in this subgroup were from the thrombolysis era. There was no difference in non-fatal MI or all-cause mortality in both subgroups.

Conclusion: We find evidence of improved clinical outcome in terms of less heart failure in STEMI patients administered intracoronary adenosine as an adjunct to reperfusion. This finding will need to be confirmed in a large adequately powered prospective RCT.

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1. Introduction

Despite reperfusion by primary percutaneous coronary intervention (PCI), the morbidity and mortality of ST-segment elevation myocardial infarction (STEMI) patients remain significant. This may be, in part, due to the presence of “myocardial reperfusion injury,” the term given to the tissue injury and cardiomyocyte death, which occurs on reperfusing previously ischemic myocardium and which contributes up to 50% of the final myocardial infarct (MI) size [1,2]. Crucially, there is currently no effective therapy for preventing myocardial reperfusion injury, and as such novel therapies are required to target myocardial reperfusion injury so as to reduce MI size and preserve left ventricular systolic function thereby preventing the onset of heart failure.

Experimental studies have established that administering adenosine prior to index ischemia can reduce MI size in animal models of acute ischemia/reperfusion injury [3], but whether adenosine can also reduce MI size when administered at the time of reperfusion has been less clear [4,5]. Although treatment with adenosine as an adjunct to reperfusion has been shown to prevent coronary no-reflow in STEMI patients, whether it can also limit MI size and improve clinical outcomes in this setting has been inconclusive [6–18]. Previous meta-analyses [19–21] have failed to find any benefit of adjunctive therapy with adenosine...
on clinical outcomes in STEMI patients. However, these meta-analyses did not include several recently published randomized control trials (RCT) [22,16–18], including two studies reporting long-term clinical outcomes [23,24]. Therefore, the aim of the current study was to perform an up-to-date meta-analysis of RCTs to determine whether adenosine administered as an adjunct to reperfusion improves clinical outcomes in STEMI patients.

2. Methods

This study was performed according to the recommendations specified in the Cochrane Handbook for Systematic Reviews of Interventions [25].

2.1. Eligibility criteria

All RCTs investigating the effect of adenosine (either intravenous or intracoronary) as an adjunct to reperfusion on clinical endpoints in STEMI patients were eligible for inclusion in the meta-analysis. RCTs comparing 3 arms were also included, provided we were able to assess data for the adenosine and control groups.

2.2. Search strategy

We searched MEDLINE and EMBASE databases up to November 2014. Additionally, we screened editorials and web-based sources of information to gain access to potential data from newly available or retrieved studies. The following search terms were used: “adenosine,” “adjunct,” “reperfusion injury,” “acute myocardial infarction,” “primary percutaneous intervention,” “randomized.” Attempt was made to contact authors of published RCTs when clinical endpoints were not reported.

2.3. Study selection

Two authors (HB, AS) identified suitable articles independently. Disagreement was resolved through consensus from a third investigator (DJH). Fig. 1 shows the process of study selection as per preferred reporting items for systematic reviews and meta-analyses (PRISMA) [26].

2.4. Data extraction and quality assessment

Baseline clinical characteristics of the study population, method of drug administration, and clinical outcome measures were extracted. Trial quality was determined as recommended by the Cochrane Handbook [25] (see Appendix A) but without constructing a composite quality score given the limitations inherent to such an approach [27]. We aimed to produce a funnel plot if there were >10 included studies in the forest plots.

2.5. Endpoints and definitions

The main clinical endpoints analyzed were all-cause mortality, non-fatal myocardial infarction, and heart failure (defined as both heart failure during the initial hospitalization or rehospitalization for heart failure). Surrogate markers of reperfusion included ST-segment resolution, TIMI coronary flow ≥3 postreperfusion, myocardial blush grade 0 or 1, and side effects of adenosine (second and third degree atrioventricular block and hypotension) were also analyzed.

2.6. Data synthesis and analysis

The RCTs were analyzed in 2 subgroups: intracoronary (IC) adenosine and intravenous (IV) adenosine. RevMan 5.2 (Nordic Cochrane Centre) was used to conduct a fixed-effect meta-analysis for the pooled risk ratio (RR), with 95% confidence intervals for dichotomous outcomes. We combined the different dose arms of adenosine in the pooled analysis against control. All reported P values are two-sided, with significance set at P < 0.05. Heterogeneity among trials was quantified using I² statistics with I² of 0–25%, 25–50% and 50–75% considered as low, moderate, and high heterogeneity, respectively.

2.7. Sensitivity analyses

If adenosine therapy showed a beneficial effect on a particular clinical endpoint, attempts were made to test the robustness of the result by removing one study at a time and looking at various subgroup analyses (trials using PPCI only; trials using thrombolysis only; trials performed after 2005 to account for changes and improvement in PPCI; excluding trials including patients presenting within 6 hours of symptoms onset only; excluding trials reporting outcomes during or after hospitalization only).

Fig. 1. PRISMA 2009 flow diagram.
Table 1
Study characteristics.

| Study and year | Clinical setting | Country | N | Adenosine dose | Follow-up | Outcomes |
|----------------|------------------|---------|---|----------------|-----------|----------|
| Intracoronary adenosine | | | | | | |
| Garcia-Dorado 2014 | STEMI undergoing PPCI | Spain | 201 | IC 4.5 mg over 2 minutes distal to the lesion immediately before thrombectomy and direct stenting | 6 months | Primary outcome: infarct size measured as total myocardial necrotic mass as determined by late enhancement on CMR imaging performed between 2 and 7 days post-reperfusion. Secondary outcomes: differences between groups in ejection fraction and ventricular volumes on the baseline CMR, in ejection fraction, infarct size, and ventricular volumes on the CMR performed at 6 months, and the difference between groups in creatine-kinase MB peak at the index episode. MACE at 1 year*: |
| Niccoli 2013/ Oct 2013 | STEMI undergoing PPCI | Italy | 160 | IC 120 µg as a fast bolus followed by 2 mg over 2 minutes following thrombus aspiration | 1 year | Primary endpoint: the incidence of ST-segment resolution >70% on surface ECG at 90 minutes after PCI Secondary endpoints: angiographic MVO incidence and MACE rate at 1 year |
| Grygier 2011/ 2013 | STEMI undergoing PPCI | Poland | 70 | IC 2 mg LCA, 1mg RCA, immediately after crossing the lesion and after first balloon inflation | 1 year | Primary endpoints: (1) ST-segment elevation resolution 60 minutes after PCI, (2) MBG at the end of procedure, and (3) final TIMI flow grade and TIMI frame count at the end of procedure. Secondary endpoints: (1) the composite endpoint of death, recurrent MI, heart failure and clinically driven TVR during 1-month follow-up, and (2) the composite endpoint of death, recurrent MI, heart failure, unplanned hospitalization for heart failure and clinically driven TVR at 1 year |
| Desmet 2011 | STEMI undergoing PPCI | Belgium | 110 | IC 4 mg bolus | 1 year | Primary endpoint: the incidence of residual ST-segment deviation > 0.2 mV, 30–60 minutes after PCI Secondary endpoint: ST-segment elevation resolution, myocardial blush grade, TIMI flow on the angiogram after PCI, enzymatic infarct size, and clinical outcome at 30 days |
| Fokkema 2009 | STEMI undergoing PPCI | Netherlands | 448 | IC 2 × 120 µg after thrombus aspiration and after stenting | 1 month | First 24 hours |
| Stoel 2008 | STEMI undergoing PPCI | Netherlands | 49 | IC 60 mg in 5–10 minutes after last balloon inflation | 1 year | ST-segment resolution and ameliorates angiographic parameters of coronary reflow (TIMI frame count, MBG, coronary blood flow, coronary vascular resistance). Follow-up for 12 months for clinical outcome Primary endpoint was the prevalence of 6-month LV remodeling Secondary endpoints were the following: (1) the prevalence of angiographic no-reflow; (2) the final corrected TIMI frame count, (3) the change in LVEDV at the 6-month follow-up |
| Petronio 2005 | STEMI undergoing PPCI | Italy | 60 | IC 4 mg before first balloon inflation | 6 months | Secondary endpoints: (1) the prevalence of angiographic no-reflow, (2) the final TIMI frame count, (3) the percentage change in LVEDV at 6 months follow-up |
| Marzilli 2000 | STEMI undergoing PPCI | Italy | 54 | IC 4 mg in 1 minute after balloon inflation | During hospitalization | Secondary endpoints: indexes of myocardial damage, including LV regional function, Q-wave MI, recurrence of angina, non-fatal MI, heart failure, and cardiac death were evaluated during hospitalization |
| Intravenous adenosine | | | | | | |
| Zhang 2012 | STEMI undergoing PPCI | China | 90 | IV 50 and 70 µg/kg/min after the guide wire crossed the lesion for 3 hours | 6 months | Primary endpoint: left ventricular function, and infarct size Secondary endpoint: occurrence of cardiac and non-cardiac death, non-fatal myocardial infarction, and heart failure at 6 months |
| Wang 2012 | STEMI undergoing PPCI | China | 69 | IV 50 µg/kg/min for 3 hours, started prior to stent implantation | 1 month | To investigate the effect of intravenous adenosine on myocardial perfusion and segmental contractile function when administered as an adjunct to PPCI Clinical outcomes were evaluated in terms of the occurrence of MACE at 1 month Primary endpoint: new CHF beginning ~24 hours after randomization, or the first rehospitalization for CHF, or death from any cause within 6 months. Infarct size was measured in a subset of 243 patients by SPECT Secondary endpoints: all-cause and cardiovascular mortality within 6 months and those specific to the infarct size sub-study |
| Ross 2005 | STEMI undergoing PCI/ thrombolysis 13 countries | | 2118 | IV 50 and 70 µg/kg/min for 3 hours to be started within 15 minutes either of the start of fibrinolysis or before coronary intervention | 6 months | Primary endpoint: global and regional left ventricular systolic and diastolic function by echocardiography Secondary endpoint: all-cause and cardiovascular mortality, and non-fatal myocardial infarction during 12 months of follow-up |
| Quintana 2003 | STEMI undergoing thrombolysis | Sweden | 608 | IV 10 µg/kg/min started with thrombolysis and maintained for 6 hours | 12 months | Primary endpoint: infarct size as determined by SPECT imaging at 6 ± 1 days Secondary endpoints: MSI and a composite of in-hospital clinical outcomes (death, re-infarction, shock, congestive heart failure, or stroke) |
| Mahaffey 1999 | STEMI undergoing thrombolysis | USA/ Canada/ Argentina | 236 | IV max 70 µg/kg/min for 3 hours before thrombolysis together with lignocaine | 4–6 weeks | Primary endpoint: feasibility and safety of intracoronary adenosine administration in the setting of primary PTCA and its effect on coronary blood flow Secondary endpoints: MSI and a composite of in-hospital clinical outcomes (death, re-infarction, shock, congestive heart failure, or stroke) |

Abbreviations: STEMI: ST-elevation myocardial infarction; PPCI: percutaneous coronary intervention; IV: intravenous; IC: intracoronary; MVO: microvascular obstruction; LV left ventricle; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; TIMI: thrombolysis in myocardial infarction; MACE: major adverse cardiovascular event; MBG: myocardial blush grade; TVR: target vessel revascularisation; LVEDV: left ventricular end diastolic volume; PTCA: primary transluminal coronary angioplasty
* Unpublished follow-up data obtained from Garcia-Dorado 2014
3. Results

3.1. Description of included studies

A total of 210 articles were retrieved from the search and 16 RCTs satisfied the predetermined inclusion criteria study review (Fig. 1). Of these, only 12 RCTs had investigated the effect of adenosine on clinical outcomes in STEMI patients. Furthermore, 1-year outcome data were obtained for the authors of the recently published PROMISE trial [22], which originally investigated the effect of intracoronary adenosine on infarct size by cardiac magnetic resonance. Two RCTs have subsequently obtained for the authors of the recently published PROMISE trial [22], and these were used for data extraction. Therefore, 8 RCTs using IC adenosine and 5 RCTs using IV adenosine were included in the meta-analysis. Table 1 shows the data extraction. Therefore, 8 RCTs using IC adenosine and 5 RCTs using IV adenosine were included in the meta-analysis. Table 1 shows the baseline characteristics of the 13 included RCTs. The study characteristics and the baseline demographics and inclusion and exclusion criteria are detailed in Table 1 and Appendices B and C.

Ji (2007) [28], Wang (2008) [29], and Akturk (2014) [30] were 3 very small trials with no clinical endpoints reported and were therefore not included in this analysis.

3.2. Quality assessment

The quality of the RCTs is shown in Appendix A. Randomization was assessed and considered adequate for 4 out of 13 trials. Although 8 of the studies were open-label, blinded observers independently adjudicated the endpoints in all of them. We did not formally test for publication bias, but we did attempt to directly contact investigators for clinical outcome data, which partly reduced the risk of publication bias.

3.3. Major clinical endpoints

The clinical endpoints are detailed in Table 2. All-cause mortality data were available for 7 out of 8 IC adenosine trials and for 4 out of 5 IV adenosine trials. Data on non-fatal MI were available for 4 out of 8 IC adenosine trials and for 3 out of 5 IV adenosine trials. There was no statistically difference in the incidence of non-fatal MI or all-cause mortality between adenosine and control for both routes of adenosine administration as shown in the Forest plots in Figs. 2 and 3. The definitions for heart failure endpoints in each trial are listed in Table 3. Heart failure outcomes were available for 5 out of the 8 IC adenosine trials and for all of the IV adenosine trials as shown in Fig. 4. There was a reduction in heart failure outcomes in the IC adenosine subgroup (RR 0.44, 95% CI 0.25–0.78, P = 0.005) but no difference in the IV adenosine subgroup (RR 1.04, 95% CI 0.81–1.33, P = 0.36).

3.4. Surrogate markers of reperfusion and safety endpoints

The details of the surrogate markers of reperfusion and safety endpoints for each trial are listed in Appendix D. Data on ST-segment resolution were available for 7 out of 8 IC adenosine trials only. However, as there was significant heterogeneity in the studies (Chi2 = 16.42, df = 6, P = 0.01; I2 = 63%), no summary effect size was estimated. Thrombolysis in myocardial infarction (TIMI) flow <3 postprocedure was available in 7 out of 8 IC adenosine trials. TIMI flow <3 postprocedure occurred with reduced incidence in the IC adenosine arm compared to control (RR 0.68 [95% CI 0.47–0.99], P = 0.04) (Fig. 5). Myocardial blush grade (MBG) of 0 or 1 was documented in 5 out of 8 IC adenosine RCTs. There was a trend toward less occurrence of MBG 0 or 1 in the adenosine group but this did not reach statistical significance (RR 0.87 [95% CI 0.70–1.08], P = 0.22) (Fig. 6). Examining these 5 studies in more detail, 400 μg of IC nitroglycerin was used in Fokkema et al. [13] in both arms prior to adenosine. Excluding this study from the analysis showed a lower incidence of MBG 0 or 1 in the adenosine group (RR 0.69, 95% CI 0.49–0.97, P = 0.03). As expected, both IV adenosine and IC adenosine were more likely to cause second and third degree heart block (IV adenosine: RR 2.86 [95% CI 1.63–5.02], P = 0.001; IC adenosine: RR 6.24 [95% CI 3.21–12.14], P = 0.001) and hypotension (IV adenosine: RR 1.19 [95% CI 1.03–1.38], P = 0.02; IC adenosine: not estimable) but these effects were transient in nature and none of the trials reported any long-lasting sequelae.

3.5. Sensitivity analyses

The reduction in the incidence of heart failure was still present in the IC adenosine subgroup despite removing one trial at a time; including trials using PPCI only (6 IC RCTs and 2 IV RCTs) and after only including trials published after 2005. This benefit persisted when only trials reporting outcomes after 6–12 months follow-up (5 IC RCTs) were considered. When trials including patients with up to 12 hours of symptoms duration were considered (6 RCTs), this benefit in heart failure reduction was no longer present but there was a trend toward less heart failure when IC adenosine trials (3 RCTs) only were considered (Appendix E).

4. Discussion

We show for the first time, improved clinical outcomes in STEMI patients administered adenosine as an adjunct to reperfusion. Our meta-analysis found that IC adenosine given at the time of PPCI reduced the incidence of heart failure in STEMI patients. This finding was associated with improved myocardial reperfusion as evidenced by a
lower incidence of coronary no-flow post-PPCI, confirmed by less postreperfusion TIMI flow <3 and less occurrence of MBG 0 or 1 (after excluding one study [13] using IC nitroglycerin in both arms prior to adenosine which itself has been shown to improve the microvascular dysfunction [31] and may have contributed to the neutral result in MBG 0 or 1 with adenosine in that study). The beneficial effects of adenosine were confined to those STEMI patients in whom adenosine was given via the IC route with no positive effects found with intravenously administered adenosine. However 3 out of 5 RCTs [6,8,11] administering IV adenosine were also confounded by the fact that they were performed in the thrombolysis era and therefore there is inadequate RCTs in this subgroup to allow us to draw any meaningful conclusion regarding IV adenosine in the PPCI setting.

In our meta-analysis, we found that IC adenosine therapy reduced the incidence of heart failure (during index admission or rehospitalization for heart failure), but there was no benefit in other major clinical endpoints of death, non-fatal MI, or revascularization. This benefit was still present despite excluding one RCT [7] in the intracoronary group looking at heart failure during hospitalization only (hospitalization for heart failure was available at 1 year for the remaining 4 RCTs [22-24,12] – Table 3) and excluding the unpublished follow-up data from the PROMISE trial [22]. The beneficial effect of adenosine on heart failure most likely relates to the impact of adenosine therapy of preventing myocardial reperfusion injury and reducing MI size, although a favorable effect on ventricular remodeling cannot be ruled-out. Adenosine, via various adenosine receptor agonists, has been shown to reduce

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**All-cause Mortality**

| Study or Subgroup | Adenosine Events | Control Events | Total Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-----------------|---------------|--------------|-----------------------------|-----------------------------|
| **1.4.1 Intravenous** |                 |               |              |                             |                             |
| Desset 2011       | 2               | 2             | 6            | 0.96 (0.90, 1.03)            |                             |
| Yokkawa 2009      | 2               | 2             | 5            | 1.42 (0.97, 2.06)            |                             |
| Garcia-Dorado 2014| 4               | 4             | 13           | 0.85 (0.34, 2.12)            |                             |
| Gygric 2013       | 0               | 0             | 1            | Not estimable               |                             |
| Marzilli 2009     | 0               | 0             | 1            | Not estimable               |                             |
| Nisso 2013        | 2               | 2             | 4            | 2.08 (0.99, 4.39)            |                             |
| Petronio 2005     | 2               | 2             | 4            | 0.81 (0.36, 1.91)            |                             |
| Schiavo 2008      | 2               | 2             | 4            | 0.88 (0.44, 1.79)            |                             |
| **Subtotal (95% CI)** | 2441           | 1649          | 100.0%       | 0.87 (0.72, 1.08)            |                             |

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**Non-fatal Myocardial Infarction**

In our meta-analysis, we found that IC adenosine therapy reduced the incidence of heart failure (during index admission or rehospitalization for heart failure), but there was no benefit in other major clinical endpoints of death, non-fatal MI, or revascularization. This benefit was still present despite excluding one RCT [7] in the intracoronary group looking at heart failure during hospitalization only (hospitalization for heart failure was available at 1 year for the remaining 4 RCTs [22-24,12] – Table 3) and excluding the unpublished follow-up data from the PROMISE trial [22]. The beneficial effect of adenosine on heart failure most likely relates to the impact of adenosine therapy of preventing myocardial reperfusion injury and reducing MI size, although a favorable effect on ventricular remodeling cannot be ruled-out. Adenosine, via various adenosine receptor agonists, has been shown to reduce

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**Fig. 2.** Forest plot for all-cause mortality, adenosine v control.

**Fig. 3.** Forest plot for non-fatal MI, adenosine v control.
reperfusion injury and subsequent infarct size in animal models through the activation of the reperfusion injury salvage kinase pathway [32]. It is also known to be a potent vasodilator [33], to have anti-inflammatory properties [34] and has been implicated in the blockade of the neutrophil-mediated processes that promote microvascular obstruction [35]. Therefore, through these pleiotropic effects, adenosine can reduce infarct size and microvascular obstruction (MVO) and reduce the risk of adverse LV remodeling and heart failure.

The main strength of our study over previously published meta-analyses [19,21,20] is the inclusion of several recently published clinical outcomes studies [24,23,18,22].

The REFLO-STEMI trial [36] (240 patients) looking at the effect of IC adenosine, sodium nitroprusside, and standard therapy on infarct size and MVO by cardiovascular MRI has completed recruitment and the results from this study would add to the current evidence on the role of IC adenosine in PPCI.

5. Limitations

There are several limitations to our meta-analysis. Firstly, the duration of symptoms varied among the RCTs, which may have diluted any beneficial effect observed with adenosine. Although we did attempt to explore trials including patients presenting within 6 hours of symptom onset, the majority of patients recruited within that time frame were confounded by also being treated by thrombolysis. Secondly, the dose of IV and IC adenosine differed greatly between studies (Table 1), and so it is difficult to ascertain the optimal IC dose of adenosine that had the most benefit. Thirdly, the timing of adenosine administration varied between studies ranging from initiating the IV infusion prior to reperfusion, and others administering the IC injection after the last balloon inflation. Finally, the RCT Stoel 2008 [12] only included patients with suboptimal ST-segment resolution and used a very high dose of IC adenosine. However, this was a small study and did not weigh significantly in the various analyses.

6. Conclusion

In summary, our meta-analysis shows for the first time that IC adenosine administered as an adjunct to reperfusion can improve clinical outcome as evidenced by a reduction in the incidence of heart failure in STEMI patients. The findings from this study are especially important for STEMI patients given the fact that despite recent reductions in mortality, the incidence of heart failure in this patient group is increasing. We hope that the findings from our meta-analysis will add to the positive evidence supporting the benefits of adenosine as an adjunct to reperfusion in STEMI patients and pave the way for large-scale prospective RCTs to confirm this beneficial effect of adenosine on major clinical outcomes.

Disclosures

No conflict of interests or relationship with industry exists.

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Table 3
Heart failure time points.

| Study               | Heart failure                                                                 |
|---------------------|-------------------------------------------------------------------------------|
| Garcia-Dorado 2013 | Hospitalization for heart failure at 1 year *                                 |
| Niccoli 2013/Oct 2013 | Not clearly defined. Heart failure at 1 year                                 |
| Grygier 2011/2013   | Heart failure during hospitalization                                          |
| Stoel 2008          | Heart failure at 1 month                                                      |
| Marzilli 2000       | Heart failure during hospitalization                                          |
| Zhang 2012          | Heart failure during hospitalization                                          |
| Wang 2012           | Heart failure during hospitalization                                          |
| Ross 2005           | Heart failure during hospitalization and rehospitalization for heart failure during 6 months |
| Quintana 2003       | Heart failure during hospitalization                                          |
| Mahaffey 1999       | Heart failure during hospitalization                                          |

* Unpublished follow-up data obtained from Garcia-Dorado 2014.

Fig. 4. Forest plot for heart failure, adenosine v control.
Appendix A. Quality assessment of included RCTs

| Study                  | Randomization sequence generation (was the method of generating the random sequence stated?) | Allocation concealment (following randomization, was allocation of intervention satisfactorily concealed, e.g. remote or centralized center, sealed opaque envelopes?) | Blinding of participants, personnel, and outcome (what type of blinding, and any specific detail on who was blinded?) | What percentage of patients was lost to follow-up? | Missing outcome data (were there any prespecified outcomes in the methods section that the authors said they would assess and report, but we were unable to extract the data for?) |
|------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------|
| Garcia-Dorado 2014    | The randomization sequence was performed in permuted block sizes of 5 and 5.                | NA                                                                                                                             | Double blinded                                                                                                    | 17 patients                                    | NA                                                                                               |
| Niccoli 2013/ Oct 2013 | Through an envelope opened by a trainee                                                      | NA                                                                                                                             | Open label                                                                                                      | 2 patients                                     | NA                                                                                               |
| Grygier 2011/ 2013     | NA                                                                                           | NA                                                                                                                             | Blind examination                                                                                                | NA                                            | NA                                                                                               |
| Desmet 2011            | Computer-generated randomization                                                             | List kept in a sealed envelope hospital pharmacy                                                                             | Double blinded                                                                                                    | NA                                            | Data on major adverse cardiac events not presented                                               |
| Fokkema 2009           | NA                                                                                           | NA                                                                                                                             | Open label trial with blinded evaluation of endpoints                                                            | NA                                            | NA                                                                                               |
| Stoel 2008             | NA                                                                                           | NA                                                                                                                             | Double blinded                                                                                                    | 1 (+1 cross-over) patients                     | NA                                                                                               |
| Petronio 2005          | Randomization in a sequential alternating fashion                                            | NA                                                                                                                             | Blinded evaluation of endpoints                                                                                   | NA                                            | NA                                                                                               |
| Marzilli 2000          | NA                                                                                           | NA                                                                                                                             | Blinded evaluation of angiograms                                                                                   | NA                                            | NA                                                                                               |
| Zhang 2012             | NA                                                                                           | NA                                                                                                                             | Blinded evaluation of cardiac echo and perfusion imaging                                                        | <20%                                           | NA                                                                                               |
| Wang 2012              | NA                                                                                           | NA                                                                                                                             | Blinded evaluation of clinical and angiographic data                                                              | NA                                            | NA                                                                                               |
| Ross 2005              | NA                                                                                           | NA                                                                                                                             | Double blinded                                                                                                    | NA                                            | NA                                                                                               |
Appendix A. (continued)

| Study                | Randomization sequence generation (was the method of generating the random sequence stated?) | Allocation concealment (following randomization, was allocation of intervention satisfactorily concealed, e.g. remote or centralized center, sealed opaque envelopes?) | Blinding of participants, personnel, and outcome (what type of blinding, and any specific detail on who was blinded?) | What percentage of patients was lost to follow-up? | Missing outcome data (were there any prespecified outcomes in the methods section that the authors said they would assess and report, but we were unable to extract the data for?) |
|----------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Quintana 2003        | NA                                                                                         | NA                                                                                                                                  | Double blinded Blinded evaluation of imaging studies                                                                                           | 2 patients NA                                                                 | NA NA                                                                                                                                         |
| Mahaffey 1999        | NA                                                                                         | NA                                                                                                                                  | NA                                                                                                                                             | NA                                                                                                                                     | NA                                                                                                                                         |

Appendix B. Baseline demographics

| Study                  | Number of patients in adenosine group | Number of patients in control group | Follow-up | Age (mean) | Male (%) | Smoker (%) | Diabetes mellitus (%) | Prior MI (%) | LAD occlusion (%) | Proximal occlusion (%) | Pre-PCI TIMI 0/1 (%) |
|------------------------|---------------------------------------|-------------------------------------|------------|------------|-----------|-------------|----------------------|---------------|-------------------|------------------------|---------------------|
| Garcia-Dorado 2014     | 100                                   | 97                                  | 6 months   | 59         | 86        | 52          | 15                   | NA            | NA                | NA                     | 100                 |
| Niccoli 2013/Oct 2013  | 80                                    | 80                                  | 1 year     | 64         | 76        | 58          | 23                   | 22            | 46                | 50                     | 86 (TIMI 0)          |
| Gryger 2011/2013       | 35                                    | 35                                  | 1 year     | 65         | 62        | 50          | 23                   | 10            | 19                | NA                     | All patients TIMI 0-2 pre-PCI |
| Desmet 2011            | 56                                    | 54                                  | 1 year     | 61         | 82        | 49          | 10                   | 1             | 41                | NA                     | 72                  |
| Fokkema 2009           | 226                                   | 222                                 | 1 month    | 62         | 75        | 58          | 10                   | 8             | 40                | 61                     | 100                 |
| Stoel 2008             | 27                                    | 27                                  | 1 year     | 67         | 66        | 36          | 11                   | NA            | 51                | NA                     | NA                  |
| Petronio 2005          | 30                                    | 30                                  | 6 months   | 58         | 85        | 52          | 20                   | NA            | 58                | 100                    | NA                  |
| Marzilli 2000          | 27                                    | 27                                  | During hospitalization | 60         | 80        | NA          | NA                   | 13            | 52                | NA                     | NA                  |
| Zhang 2012             | 59                                    | 31                                  | 6 months   | 63         | 81        | 59          | 33                   | NA            | 47                | 96.3% of patients TIMI 0-2 pre-PCI |
| Wang 2012              | 35                                    | 34                                  | 1 month    | 57         | 83        | 46          | 19                   | 0             | 65                | NA                     | NA                  |
| Ross 2005              | 1415                                  | 703                                 | 6 months   | 60         | 73        | NA          | 16                   | 13            | 100               | NA                     | NA                  |
| Quintana 2003          | 302                                   | 306                                 | 12 months  | 65         | 76        | 32          | 9                    | 23            | NA                | NA                     | NA                  |
| Mahaffey 1999          | 119                                   | 117                                 | 4-6 weeks  | 58         | 72        | 81          | 22                   | 15            | 39                | NA                     | NA                  |

Abbreviations: MI: myocardial infarction; LAD: left anterior descending artery; PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction.

Appendix C. Inclusion and exclusion criteria

| Study                  | Inclusion criteria                                                                 | Exclusion criteria                                                                                                                                                                                                                     |
|------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Garcia-Dorado 2014     | Over 18 years of age with a diagnosis of STEMI on ECG and receiving PCI within 6 hours of symptom onset. | Previous myocardial infarction and TIMI flow grade 1 on initial angiography. Patients with potential contraindications for adenosine and contraindications for MIBI examination or for gadolinum administration (renal function b30 mL/min/1.73 m2) or those with life expectancy of less than 6 months. Age b18 years, previous STEMI in the same territory of current admission, cardiogenic shock, pregnancy, history of renal failure (serum creatinine b3 mg/dL), contraindications to contrast agents or other study medications, paced rhythm, frequent ventricular ectopy, left bundle branch block, pre-excitation or other conditions or artifacts interfering with interpretation of the ST segment, culprit lesion located in a bypass graft, stent thrombosis, unidentified culprit lesion, and left main disease. |
| Niccoli 2013/Oct 2013  | Symptom onset b12 hours before enrolment, ST-segment elevation of at least 2 mm in 2 or more contiguous leads, and thrombolysis in myocardial infarction (TIMI) flow grade 0/1 at baseline angiography. | TIMI flow 3, patients with chronic obstructive pulmonary disease or asthma and those who had received previous thrombolysis were excluded. Age b18 years, previous STEMI in the same territory of current admission, cardiogenic shock, pregnancy, history of renal failure (serum creatinine b3 mg/dL), contraindications to heparin, low-molecular-weight heparin or clopidogrel, anticipated difficult vascular access, cardiogenic shock, inability to give informed consent, high-grade atrioventricular block, severe asthma, treatment with theophylline, glibenclamide, or dipyridamole, prior coronary artery surgery, and participation in any investigational drug or device study within the past 6 months. |
| Gryger 2011/2013       | 6 hours of symptom onset, TIMI flow 0–2                                             | Contraindication to heparin, low-molecular-weight heparin or clopidogrel, anticipated difficult vascular access, cardiogenic shock, inability to give informed consent, high-grade atrioventricular block, severe asthma, treatment with theophylline, glibenclamide, or dipyridamole, prior coronary artery surgery, and participation in any investigational drug or device study within the past 6 months. |
| Desmet 2011            | Cardiac sounding chest pain of at least 20 minutes x, a time from onset of symptoms of b12 hours, and an ECG showing ST-segment elevation of .01 mV in two or more limb leads or .02 mV in two or more contiguous precordial leads, or presumed new left bundle-branch block. | The presence of cardiogenic shock, existence of a life-threatening disease with a life expectancy of b6 months, receiving pharmacotherapy for chronic obstructive pulmonary disease, or no informed consent. |
| Fokkema 2009           | Symptoms of chest pain suggestive for myocardial ischemia for at least 30 minutes, a time from onset of symptoms of b12 hours before hospital admission, and an ECG showing ST-segment elevation of b0.1 mV in 2 or more leads. | Excluded were patients with hemodynamic instability, prior myocardial infarction or an ECG unsuitable for calculation of STRes (left bundle branch block, paced or severe disturbed rhythm). In addition, patients with a history of obstructive pulmonary disease were excluded because of potential side effects of adenosine. |
| Stoel 2008             | Following successful (defined as TIMI flow grade 2 or 3 without residual dissections or stenosis b30% and no angiographic evidence of embolisation) PCI for acute myocardial infarction, patients with suboptimal reperfusion (b70% STRes with persistent ST-elevation b2 mV in at least one anterior lead and b1 mV in a non-anterior lead) more than 10 minutes after last balloon inflation could be included. | (continued on next page) |
### Appendix D. Angiographic, electrographic, and adenosine related side effects

| Study            | Angiographic data | Electrographic data | Adenosine related side effects |
|------------------|-------------------|---------------------|--------------------------------|
|                  | Postprocedural TIMI flow | STEMI resolution on ECG | Bradycardia | Hypotension |
|                  | Adenosine | Placebo | Adenosine | Placebo | Adenosine | Placebo | Adenosine | Placebo | Adenosine | Placebo | Adenosine | Placebo |
|                  | Adenosine | Placebo | Adenosine | Placebo | Adenosine | Placebo | Adenosine | Placebo | Adenosine | Placebo | Adenosine | Placebo |
| García-Dorado 2014 | 6 12 0 3 3 0 15 15 | 69 45 5 4 2 1 0 0 | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA |
| Niccol 2013/ Oct 2013 | 7 8 NA NA 7 16 57 41 | 1 0 11 2 5 7 | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA |
| Grypiet 2011/ 2013 | 3 8 0 3 5 9 27 15 | 8 0 NA NA 0 0 | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA |
| Desnet 2011 | 11 7 NA NA 19 21 25 21 | 5 7 13 5 NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA |
| Fokkema 2009 | 13 14 2 1 70 66 154 147 | 34 5 31 2 24 2 | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA |
| Stoei 2008 | NA NA NA NA NA NA NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA |
| Petronio 2005 | 2 4 4 5 NA NA 13 16 | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA |
| Marzilli 2000 | 0 8 1 7 NA NA NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA |NA NA |
| Zhang 2012 | 1 4 3 11 2 9 NA NA | 7 1 12 1 12 3 | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA |
| Wang 2005 | 4 5 NA NA NA NA NA NA | 38 16 56 7 263 98 | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA |
| Quintana 2003 | NA NA NA NA NA NA NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA |
| Mahaffey 1999 | NA NA NA NA NA NA NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA | NA NA |

Abbreviations: MBG: myocardial blush grade; TIMI: thrombolysis in myocardial infarction; STRes: ST-segment resolution; STEMI: ST-elevation myocardial infarction; TIMI: thrombolysis in myocardial infarction.
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