Review

Adenosine improves post-procedural coronary flow but not clinical outcomes in patients with acute coronary syndrome: A meta-analysis of randomized trials

Eliano Pio Navarese [a,d,∗], Antonino Buffon [b], Felicita Andreotti [b], Paul Alfred Gurbel [c], Marek Kozinski [a], Aldona Kubica [e], Giuseppe Musumeci [f], Alberto Cremonesi [a], Luigi Tavazzi [a], Jacek Kubica [d], Fausto Castriota [a]

[a] Interventional Cardio-Angiology Unit, GVM Care and Research, Cotignola, RA, Italy
[b] Department of Cardiovascular Medicine, Catholic University of the Sacred Heart, Rome, Italy
[c] Sinai Center for Thrombosis Research, Sinai Hospital of Baltimore, Baltimore, MD, USA
[d] Department of Cardiology and Internal Medicine, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[e] Department of Health Promotion, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[f] Department of Cardiovascular Medicine, Ospedali Riuniti, Bergamo, Italy

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ABSTRACT

Aims: Adjunctive therapy with adenosine has been shown to improve coronary flow in patients with acute coronary syndromes (ACS); it is unclear, however, whether adenosine can effectively reduce adverse clinical events. The aim of our study was to perform a meta-analysis of all randomized controlled trials (RCTs) investigating angiographic and clinical outcomes in ACS patients undergoing PCI or thrombolysis and receiving adjunctive adenosine therapy vs. placebo.

Methods: Medline/CENTRAL/EMBASE and Google Scholar database were scanned. The meta-analysis included ten RCTs ($N = 3821$). All-cause mortality was chosen as primary endpoint. Secondary endpoints were re-infarction (MI), heart failure (HF) symptoms (NYHA class III/IV), no-reflow (defined as TIMI 0 flow) and >50% ST-resolution.

Results: Adenosine compared to placebo was associated with a significant reduction of post-procedural no-reflow (OR [95% CI] = 0.25 [0.08–0.73], $p = 0.01$); however, at a median follow-up of 6 months, prior treatment with adenosine did not confer significant benefits in terms of reduction of mortality (OR_{Fixed} [95% CI] = 0.87 [0.69–1.09], $p = 0.23$), as well as re-MI ($p = 0.80$), HF symptoms ($p = 0.44$) and ST-resolution ($p = 0.09$). Separate analyses conducted in the subgroups of ST-elevation MI patients treated with either PCI or thrombolysis confirmed the findings found in the overall population.

Conclusions: This meta-analysis shows that adenosine adjunctive therapy does not improve survival nor reduce the rates of re-MI and HF symptoms in patients with ACS treated with PCI or thrombolysis. The beneficial effect on post-procedural coronary flow was not associated with consistent advantages on clinical outcomes.

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Contents

1. Introduction

The cornerstone of treatment of patients with acute coronary syndrome (ACS), especially those with ST-segment elevation myocardial infarction (STEMI), is to promptly restore myocardial blood flow and thus limit infarct size. Reperfusion is generally achieved pharmacologically by thrombolysis or mechanically by percutaneous coronary intervention (PCI). Although most patients treated with PCI or thrombolysis achieve epicardial coronary artery patency, effective myocardial reperfusion may not occur due to a myocardial injury phenomenon known as no-reflow [1]. Small studies in STEMI patients [2,3] have suggested that adenosine improved microvascular function, reducing the occurrence of no re-flow. Several recent randomized studies, investigating whether adenosine might reduce the incidence of adverse clinical outcomes among ACS patients, have yielded conflicting results. The aim of the current study was to perform a meta-analysis of all available randomized controlled trials (RCTs) comparing the effect of adenosine vs. placebo on clinical outcomes in ACS patients treated with PCI or thrombolysis.

2. Methods

The present meta-analysis was performed according to established methods of the Cochrane guidelines [4] and in compliance with the PRISMA statement for reporting systematic reviews and meta-analyses in health care interventions [5].

2.1. Search strategy

A search covering the period from January 1993 to August 2011 was conducted by two independent investigators using MEDLINE, CENTRAL, EMBASE and Google Scholar databases. Proceedings from the Scientific Sessions of the American College of Cardiology [http://www.acc.org], American Heart Association [http://www.aha.org], European Society of Cardiology [http://www.escardio.org], Transcatheter Cardiovascular Therapeutics [http://www.tctmd.com] and EuroPCR [http://www.europcr.com] were also considered. The following keywords were applied: "adenosine"; "acute coronary syndrome"; "ST-elevation myocardial infarction (STEMI)"; "randomized". References of retrieved studies were searched manually for additional trials. No language restrictions were applied.

2.2. Selection criteria

Citations were screened at title/abstract level and retrieved as full reports. Inclusion criteria were: (1) human studies; (2) randomized administration of adenosine vs. placebo; (3) ACS treated with PCI or thrombolysis; (4) systematic reporting of clinical outcomes. Exclusion criteria were: – studies comparing adenosine vs. placebo during elective PCI or in the setting of bypass surgery; – observational studies; – studies comparing the use of a compound similar to adenosine but with different chemical properties; – lack of placebo arm; – RCTs not reporting clinical outcomes. The internal validity of each study was appraised by two unblinded investigators according to proper allocation sequence/concealment, patient blinding, investigator blinding, and completeness of outcome data/full reporting. Prespecified abstracted data were: study/trial name, journal (year), number of adenosine- and placebo-treated patients, maximum follow-up time available, clinical setting, route and dose of adenosine administration, treatment strategy, and ischaemic time, defined as time from symptom onset to start of treatment (PCI or thrombolysis).

2.3. Study endpoints

The primary chosen endpoint was all-cause mortality. Secondary endpoints were the incidence of no-reflow (defined as TIMI 0 flow according to the TIMI definition), re-MI, heart failure symptoms (NYHA class III–IV), and ST-resolution, defined as post-procedural resolution ≥50%.

2.4. Statistical analyses

Odds ratio (OR) and 95% confidence intervals (95% CI) were used as summary statistics. Heterogeneity was assessed by Cochran's Q test, with a 2-tailed $p = 0.1$, as conventionally recommended [6]. Statistical inconsistency test (I2) $[(Q - df)/Q] \times 100\%$, where Q is the chi-squared statistic and df is its degrees of freedom, was also employed to overcome the low statistical power of Cochran's Q test [7]. The pooled OR was calculated using a fixed-effect model with the Mantel–Haenszel method. The DerSimonian and Laird random effects model was used in case of significant heterogeneity and/or moderate or significant inconsistency (>50%) across studies. Potential publication bias was examined by constructing a 'funnel plot', in which the standard error (SE) of the ln OR was plotted against the OR (for mortality or re-MI or re-PCI) [8]. In addition, a mathematical estimate of the asymmetry of this plot was provided by a linear regression approach [9]. All analyses were performed according to the intention-to-treat principle. A 2-tailed p value <0.05 was considered significant.

3. Results

3.1. Eligible studies

Ten RCTs [10–15,3,16–18], involving 3821 patients, met the inclusion criteria and were included in the meta-analysis (Fig. 1).
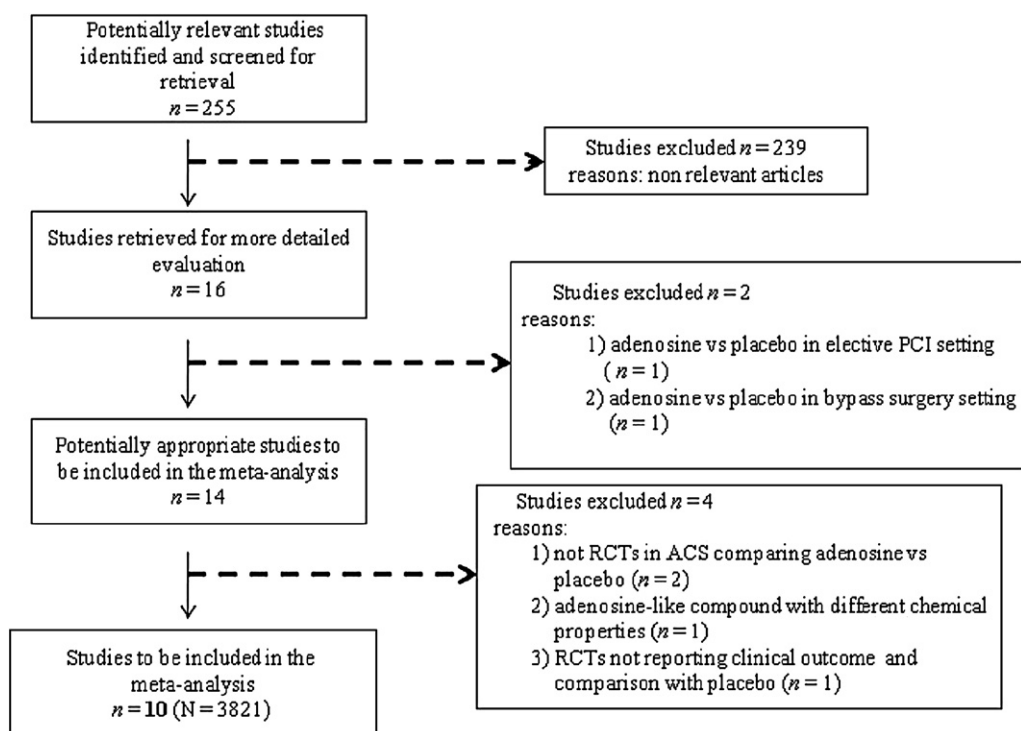
Fig. 1. Flow chart of the meta-analysis according to the PRISMA statement.

The main study characteristics are listed in Table 1. All eligible trials investigated the use of adenosine in STEMI patients, except for one [19] which included a mixed patient population (non-STEMI and STEMI). The median follow-up was 6 months. In the AMIS-TAD (*Acute Myocardial Infarction STudy of ADenosine*) I and II and in the ATTACC (*ATTenuation by Adenosine of Cardiac Complications*) trials, adenosine was administered after thrombolysis through the intravenous route; in the remaining seven trials, intracoronary (IC) adenosine was given during PCI. The patients from the AMIS-TAD II trial included in the meta-analysis were those treated with the highest dose of adenosine (70 μg/kg/min), compared to those receiving placebo.

Table 1
Summary of randomized studies comparing adenosine vs. placebo in patients with acute coronary syndrome; h = hours; IC = intracoronary adenosine; IV = intravenous adenosine; na = not available; NSTEMI = non ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; pts = patients.

| Study	Journal (year)	Adenosine + placebo pts	Follow-up time (months)	Setting	Route of adenosine	Dose of adenosine	Treatment strategy	Ischemic time before treatment (min)
AMISTAD-I [10]	JACC (1999)	236	1.4	STEMI	IV	70 μg/kg/min for 3 h	Thrombolysis	111
AMISTAD -II [11]	JACC (2005)	2117	6	STEMI	IV	70 μg/kg/min for 3 h	Thrombolysis	195
ATTACC [12]	Eur J Clin Pharmacol (2003)	608	12	STEMI	IC	10 μg/kg/min for 6 h	Thrombolysis	208
Desmet [13]	Eur Heart J (2011)	112	1.12	STEMI	IC	4 mg quickly administered	PCI	215
Fokkema [14]	Circ Cardiov Intervent (2009)	448	1	STEMI	IC	2 × 120 μg in 20 mL 0.9% NaCl	PCI	180
Grygier [15]	Am J Cardiol (2011)	70	1	STEMI	IC	2 mg to the left artery, 1 mg to the right artery in ~1 min	PCI	270
Marzilli [16]	Circulation (2000)	54	In-hospital	STEMI	IC	4 mg in ~1 min	PCI	106
Stoel [3]	Catheter Cardiovasc Interv (2008)	49	12	STEMI	IC	60 mg in 5–10 min	PCI	196
Tian [17]	Chiense Medical J (2008)	26	1	STEMI	IC	2 mg/min for 10 min	PCI	na
Vijayalakshmi [18]	Heart (2006)	101	6	NSTEMI, STEMI	IC	30 μg in 10 ml of heparinised saline	PCI	na
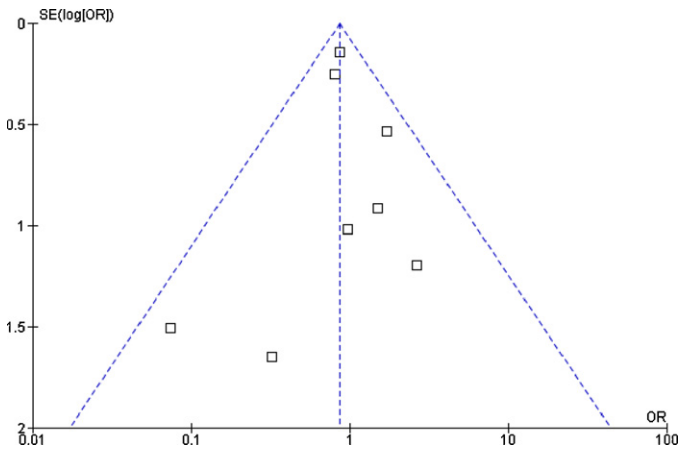
Fig. 2. Funnel plot for the mortality outcome. The sample size of each study (measured as standard error of the treatment effect) was plotted against the odds ratio for overall mortality. One study (Tian) did not report mortality data; in another (Grygier), the odds ratio was not estimable for lack of events.

3.2. Mortality

As shown in Fig. 2, no publication bias was found, and this was confirmed by Egger's test which was non significant.

Nine randomized studies, involving a total of 3793 patients, reported the incidence of death in those allocated to adenosine ($N = 2257$) or placebo ($N = 1536$). There were a total of 335 deaths. The incidence of death was 8.7% (196/2257) in the adenosine group and 9.0% (139/1536) in the placebo group. The overall results showed no significant benefit with adenosine therapy as compared to placebo in reducing mortality (OR_{Fixed} [95% CI] = 0.87 [0.69–1.09], $p = 0.23$; p heterogeneity = 0.55; Fig. 3). These results were confirmed when analyzing the STEMI population only: OR_{Fixed} [95% CI] = 0.89 [0.72–1.09], $p = 0.25$.

3.3. Secondary endpoints

3.3.1. No-reflow

There was no evidence of publication bias, with a non significant Egger's test. Five randomized studies ($N = 865$) reported the rates of no-reflow after administration of adenosine or placebo. Adenosine markedly reduced the incidence of post-procedural no-reflow as compared to placebo (0.7% vs. 3.5%; OR_{Fixed} [95% CI] = 0.23 [0.08–0.70], $p = 0.01$; p heterogeneity = 0.24; Fig. 4).

A significant reduction of no reflow was also observed when considering the STEMI population only: OR_{Fixed} [95% CI] = 0.22 [0.07–0.72], $p = 0.01$.

Fig. 3. Forest plot of adenosine vs. placebo for all-cause mortality; overall and individual odds ratios and 95% confidence intervals (CI) are reported. The size of the data markers (squares) is proportional to the statistical weight of each trial.

Fig. 4. Forest plot of adenosine vs. placebo for no-reflow; overall and individual odds ratios and 95% confidence intervals (CI) are reported. The size of the data markers (squares) is proportional to the statistical weight of each trial.
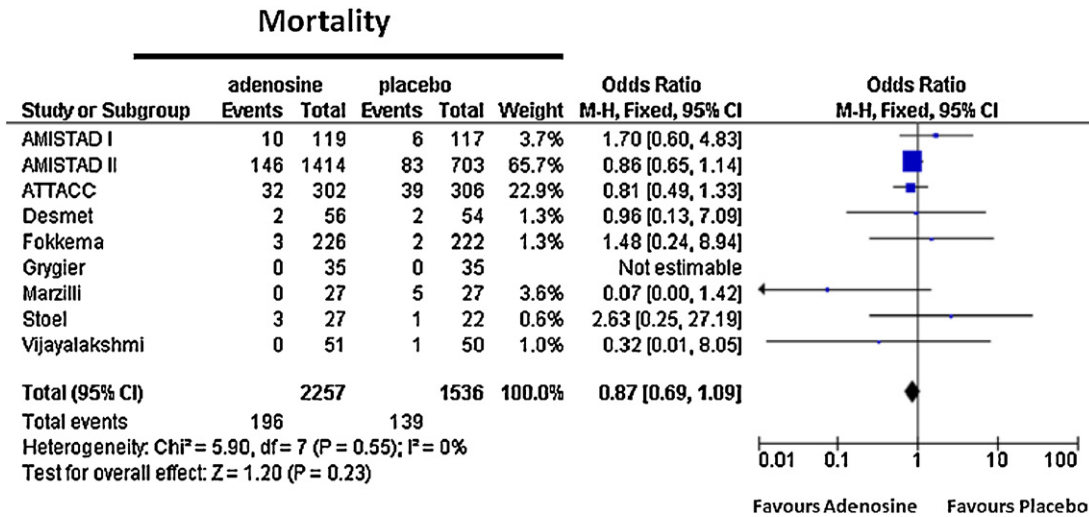
Re-infarction

Fig. 5. Forest plot of adenosine vs. placebo for re-infarction; overall and individual odds ratios and 95% confidence intervals (CI) are reported. The size of the data markers (squares) is proportional to the statistical weight of each trial.

Heart failure

Fig. 6. Forest plot of adenosine vs. placebo for heart failure symptoms (NYHA class III-IV); overall and individual odds ratios and 95% confidence intervals (CI) are reported. The size of the data markers (squares) is proportional to the statistical weight of each trial.
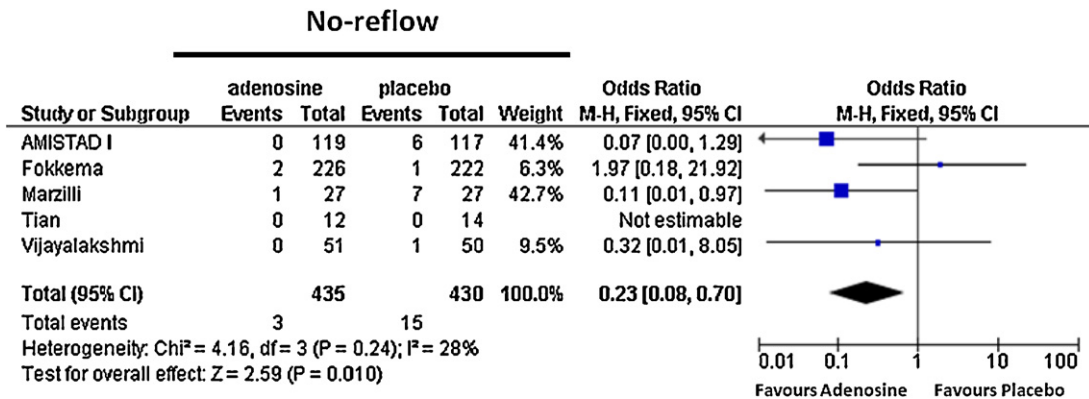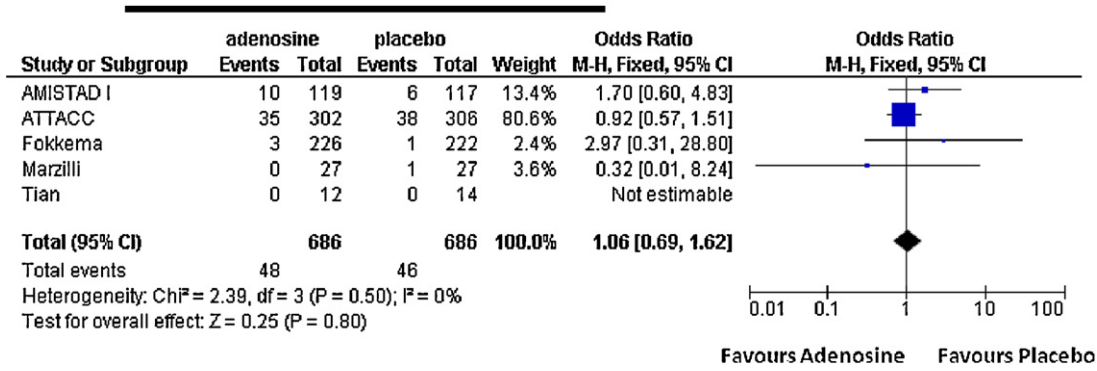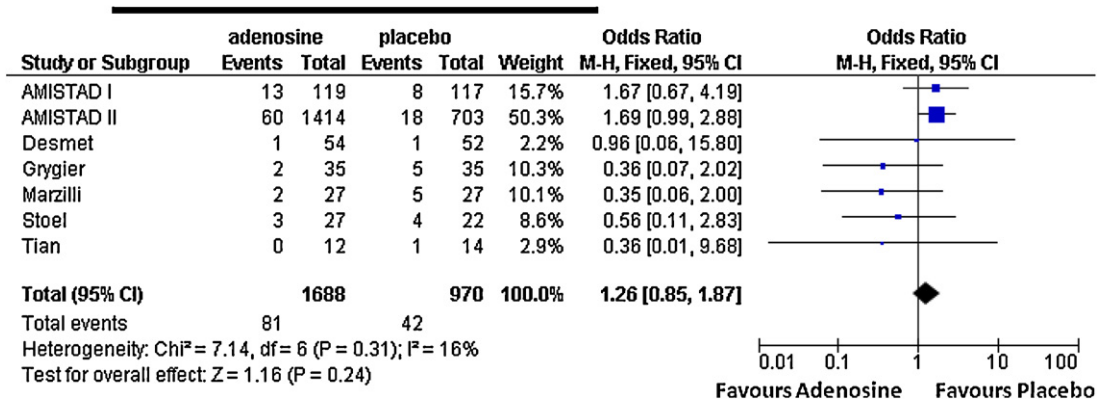
3.3.2. Re-infarction

Among 1372 patients, there were 94 re-MIs over the long-term follow up. The incidence of MI was 6.9% (48 out of 686 patients) in the adenosine group and 7.0% (46 out of 686) in the placebo group (OR_{Fixed} [95% CI] = 1.06 [0.69–1.62], p = 0.80; p heterogeneity = 0.50; Fig. 5).

3.3.3. Heart failure

As shown in Fig. 6, the rates of heart failure symptoms (NYHA class III–IV) were highly comparable between the adenosine and placebo arms, without any significant benefit in symptom relief by adenosine treatment: 4.8% (81/1688) vs. 4.3% (42/970): OR_{Fixed} [95% CI] = 1.26 [0.85–1.87], p = 0.24; p heterogeneity = 0.31).
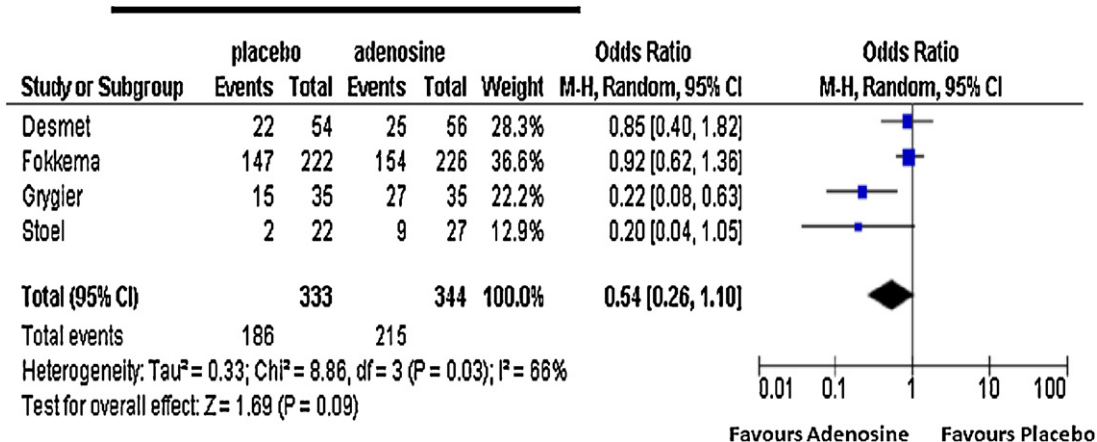
ST-resolution

Fig. 7. Forest plot of adenosine vs. placebo for ST-segment resolution; overall and individual odds ratios and 95% confidence intervals (CI) are reported. The size of the data markers (squares) is proportional to the statistical weight of each trial.
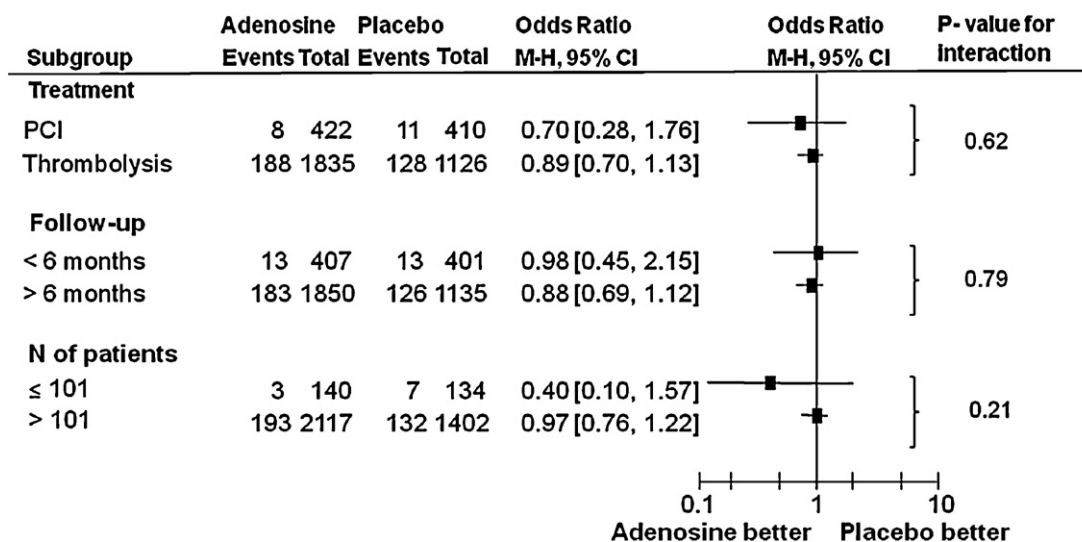
Subgroup	Adenosine Events Total	Placebo Events Total	Odds Ratio M-H, 95% CI	Odds Ratio M-H, 95% CI	P- value for Interaction
Treatment					
PCI	8 422	11 410	0.70 [0.28, 1.76]		
Thrombolysis	188 1835	128 1126	0.89 [0.70, 1.13]		0.62
Follow-up					
< 6 months	13 407	13 401	0.98 [0.45, 2.15]		
> 6 months	183 1850	126 1135	0.88 [0.69, 1.12]		0.79
N of patients					
≤ 101	3 140	7 134	0.40 [0.10, 1.57]		
> 101	193 2117	132 1402	0.97 [0.76, 1.22]		0.21

0.1   1   10
Adenosine better   Placebo better

Fig. 8. Forest plot of adenosine vs placebo for overall mortality in 3 predefined subgroups: treatment with PCI vs. thrombolysis, follow-up < vs. > 6 months, number of enrolled patients ≤ 101 vs. > 101 patients. Individual odds ratios with 95% confidence intervals (CI) are reported, with the related p value for their interaction.

3.3.4. ST-segment resolution

Four studies reported the incidence of ≥50% ST-segment resolution after intracoronary adenosine vs. placebo. Patients treated with intracoronary adenosine showed a non-significant trend towards greater ST-segment resolution compared to the patients in the placebo group: 62.5% (215/344) vs. 52.9% (186/333), OR_{Random} [95% CI] = 0.54 [0.26–1.10], $p = 0.09$; p heterogeneity = 0.03; Fig. 7).

3.4. Sensitivity analyses

Several sensitivity analyses were conducted to formally explore the robustness of the results. The sensitivity analysis performed by removing each of the studies one at a time did not demonstrate any single study to influence the overall results for any of the chosen outcomes. Stratified analysis showed no significant differences in mortality rates between: (1) studies in which the treatment strategy was PCI (where IC adenosine was given) and studies in which thrombolysis was used (where adenosine was administered intravenously; p for interaction = 0.62); (2) studies reporting a follow-up < or > 6 months (p for interaction = 0.79); (3) studies enrolling a total number of patients >101 or >101 patients (p interaction = 0.21) (Fig. 8). Sensitivity analysis, performed by including each of the studies one at a time according to increasing dose of IC adenosine, from the lowest to the highest (up to 60 mg), showed that different doses did not influence any of the clinical outcomes investigated, as well. The different burden of ischaemic time across the various studies did not influence the results, as shown in the sensitivity analyses where the inclusion of studies with variable ischaemic time from the lowest to the highest did not change the magnitude and direction of the overall results for all the outcomes chosen. Finally, the analyses conducted only in the STEMI population, by removing the study in which a mixed population (non-STEMI and STEMI) was enrolled, confirmed the results found in the overall population for all of the outcomes.

4. Discussion

Cardiovascular disease remains the biggest killer in the developed world, with the majority of morbidity and mortality attributable to the effects of ACS. The lack of effective reperfusion of the myocardium after prolonged ischaemia, that may occur despite opening of the epicardial infarct-related artery, has been attributed to the reperfusion injury termed "no-reflow". Adenosine

has been shown in animal models to potentially prevent reperfusion injury and the no-reflow phenomenon [19–21]. In vitro, adenosine exhibits energy-saving, antiplatelet, vasodilatory, anti-inflammatory, antioxidant, as well as antiarrhythmic effects [22]. Clinical studies with adenosine in ACS have yielded mixed results. AMISTAD was one of the first human studies in acute myocardial infarction [10]. It showed in 236 patients that adenosine, given as a 3-h intravenous infusion (10 μg/kg/min increasing to 70 μg/kg/min as tolerated) and commenced prior to thrombolysis with streptokinase or alteplase, did not reduce the composite clinical endpoint (death, reinfarction, shock, congestive heart failure or stroke). In the study by Marzilli et al., IC adenosine (4 mg), given as a slow hand-injection in patients undergoing emergent revascularization for acute MI with balloon angioplasty (and stenting for suboptimal balloon inflations), resulted in a decreased incidence of the no-reflow phenomenon, with improved myocardial perfusion and a more favourable clinical course, in terms of combined clinical endpoints [16]; these results, on the other hand, were not confirmed in a more recent study, even when administering higher IC adenosine doses [14]. Because none of these trials were individually powered to assess differences in clinical outcomes, a definitive conclusion on the potential clinical benefits of adenosine treatment could not be drawn.

This is the first meta-analysis comparing the angiographic and clinical effects of adenosine adjunctive therapy in the ACS population. Despite a marked fall in the incidence of no-reflow after PCI, this meta-analysis did not show any clear advantage with adenosine on the rates of all-cause mortality, re-MI or HF symptoms; these results were confirmed in sensitivity analyses conducted in the subgroups of STEMI patients treated with either primary PCI or thrombolysis. Current ESC guidelines for the management of patients with acute STEMI allow the option of an IV infusion of 70 μg/kg/min over 3 h during and after PCI (class IIb; level of evidence B) or an IC bolus of 30–60 μg adenosine during PCI (class IIb; level of evidence C) for the prevention-treatment of no-reflow [23]. The results of the present meta-analysis suggest that the improvement of coronary flow velocities shown in observational studies, as well as the significant reduction of no-reflow [2,24], may be transient vascular/rheological effects of adenosine, that do not translate into long-lasting relevant clinical benefits.

Notably, the lack of benefit on clinical outcomes with adenosine treatment observed in our meta-analysis persisted in the

sensitivity analysis by removing the studies according to increasing IC dose of adenosine, from the lowest to the highest, up to 60 mg. The lack of impact of increasing doses of adenosine on outcome is relevant, prompting caution in administering very high IC doses, as this caution may reduce the frequency and severity of side effects associated with the drug, such as bradycardia and hypotension, that are dose-dependent.

A potential reason for the lack of persistent beneficial effects of adenosine in the setting of ACS is that during myocardial ischaemia there is already a huge production of endogenous adenosine; moreover, given the extremely short half-life of this active metabolite (in the order of a few seconds) [25], exogenous adenosine may not produce lasting effects beyond the time of its administration. Indeed, the half life of adenosine in human blood may be too short to protect from oxygen free radicals, which peak at 2–3 min of reperfusion, even if reperfusion is started only 15–30 s after adenosine administration [26].

Additionally, mechanistic evidence based on short term, surrogate parameters such as coronary TIMI flow may be poor predictors of potential protective pathways; moreover, short term effects may be weak predictors of long term outcomes, especially since extrapolation problems increase with increasing extrapolation time (i.e., time difference between the effect played by adenosine and the clinical outcome).

To date the optimal management of reperfusion-related injury in ACS patients still remains a challenging question. The present meta-analysis shows that the short-term treatment with adenosine as compared to placebo is not effective in achieving significant lasting improvements in the clinical outcomes. Further RCTs testing different treatment strategies are warranted to find ways to improve both coronary flow and clinical outcomes in ACS patients.

5. Conclusions

This meta-analysis shows that adenosine, as adjunctive therapy for ACS patients, does not improve survival, nor reduce the rates of MI and HF symptoms. The beneficial effect of adenosine was confined to the improvement of post-procedural coronary flow but without consistent advantages on clinical outcomes. Similar results were observed in the STEMI subgroups treated with either PCI or thrombolysis.

6. Limitations

A limitation of this meta-analysis, common to all meta-analyses based on study-level data, is the lack of individual patient data that would have further improved the results of the current study. In particular, analysis of outcomes by time from symptom onset to adenosine/placebo administration was not possible.

The heterogeneous sample size with a small number of patients enrolled in some studies (<100) and the relatively low rate of clinical events are some limitations inherent to the included studies; the meta-analysis therefore might have a low power compared to a larger randomized trial; the variance of single odds ratios across the studies also suggests caution in interpreting the results; on the other hand, the stability of the results after performing sensitivity analyses for all the outcomes chosen (including mortality as the primary endpoint) (cfr sensitivity analysis paragraph) and the narrower CIs associated with the overall estimates than with those pertaining to the included studies support the findings of the meta-analysis and suggest that the overall effect is justified.

Multiple causes might influence mortality and other endpoints in favour of one or another intervention in a complex population such as that of ACS patients; on the other hand, this meta-analysis is based on randomized data which should overcome or at least mitigate in the best possible way this bias. Information regarding the administration of concomitant drugs, such as glycoprotein IIb/IIIa inhibitors, was available in only one study, therefore the effect of concomitant adjunctive therapies could not be evaluated.

References

[1] Butler MJ, Chan W, Taylor AJ, Dart AM, Duffy SJ. Management of the no-reflow phenomenon. Pharmacol Ther 2011;132:72–85.
[2] Claeys MJ, Bosmans J, De Ceuninck M, et al. Effect of intracoronary adenosine infusion during coronary intervention on myocardial reperfusion injury in patients with acute myocardial infarction. Am J Cardiol 2004;94:9–13.
[3] Stoel MG, Marques KM, de Cock CC, et al. High dose adenosine for suboptimal myocardial reperfusion after primary PCI: a randomized placebo-controlled pilot study. Catheter Cardiovasc Interv 2008;71:283–9.
[4] The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions. Available at: www.cochrane.org/resources/handbook/ (accessed 24.08.11).
[5] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
[6] Fleiss JL. Analysis of data from multiclinics trials. Controlled Clin Trials 1986;7:267–75.
[7] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[8] Egger M, Smith GD, Schneider M, Minder C. Bias in metaanalysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[9] Egger M, Smith GD. Bias in location and selection of studies. BMJ 1998;31:61–6.
[10] Mahaffey KW, Puma JA, Barbagelata NA, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) Trial. J Am Coll Cardiol 1999;34:1711–20.
[11] Ross AM, Gibbons RJ, Stone GW, et al. A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). J Am Coll Cardiol 2005;45:1775–80.
[12] Quintana M, Hjemdahl P, Sollevi A, et al. Left ventricular function and cardiovascular events following adjuvant therapy with adenosine in acute myocardial infarction treated with thrombolysis, results of the ATTenuation by Adenosine of Cardiac Complications (ATTACC) study. Eur J Clin Pharmacol 2003;59:1–9.
[13] Desmet W, Bogaert J, Dubois C, et al. High-dose intracoronary adenosine for myocardial salvage in patients with acute ST-segment elevation myocardial infarction. Eur Heart J 2011;32:867–77.
[14] Fokkema ML, Vlaar PJ, Vogelzang M, et al. Effect of high-dose intracoronary adenosine administration during primary percutaneous coronary intervention in acute myocardial infarction: a randomized controlled trial. Circ Cardiovasc Interv 2009;2:323–9.
[15] Grygier M, Araszkiewicz A, Lesiak M, et al. New method of intracoronary adenosine injection to prevent microvascular reperfusion injury in patients with acute myocardial infarction undergoing percutaneous coronary intervention. Am J Cardiol 2011;107:1131–5.
[16] Marzilli M, Orsini E, Marraccini P, Testa R. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. Circulation 2000;101:2154–9.
[17] Tian F, Chen YD, Lü SZ, et al. Intracoronary adenosine improves myocardial perfusion in late reperfused myocardial infarction. Chin Med J 2008;121:195–9.
[18] Vijayalakshmi K, Whittaker VJ, Kunadian B, et al. Prospective, randomised, controlled trial to study the effect of intracoronary injection of verapamil and adenosine on coronary blood flow during percutaneous coronary intervention in patients with acute coronary syndromes. Heart 2006;92:1278–84.
[19] Babbitt DG, Virmani R, Forman MB. Intracoronary adenosine administered after reperfusion limits vascular injury after prolonged ischemia in the canine model. Circulation 1989;80:1388–99.
[20] Velasco CE, Turner M, Cobb MA, Virmani R, Forman MB. Myocardial reperfusion injury in the canine model after 40 min of ischemia: effect of intracoronary adenosine. Am Heart J 1991;122:1561–70.
[21] Teng B, Mustafa SJ. A(2A) adenosine receptor-mediated increase in coronary flow in hyperlipidemic APOE-knockout mice. J Exp Pharmacol 2011;2011:59–68.
[22] Andreotti F, Pasceri V. Ischaemic preconditioning. Lancet 1996;348:204.
[23] Van de Werf F, Bax JJ, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. Eur Heart J 2008;29:2909–45.
[24] Assali AR, Sdringola S, Ghani M, et al. Intracoronary adenosine administered during percutaneous intervention in acute myocardial infarction and reduction in the incidence of no reflow phenomenon. Catheter Cardiovasc Interv 2000;51:27–31.
[25] Shryock JC, Belardinelli L. Adenosine and adenosine receptors in the cardiovascular system: biochemistry, physiology, and pharmacology. Am J Cardiol 1997;79:2–10.
[26] Forman MB, Stone GW, Jackson EK. Role of adenosine as adjunctive therapy in acute myocardial infarction. Cardiovasc Drug Rev 2006;24:116–47.