Review

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

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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/V), 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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Abbreviations: ACS, Acute coronary syndromes; CI, confidence interval; IC, intracoronary adenosine; IV, intravenous adenosine; h, hours; HF, heart failure; na, not available; OR, odds ratio; PCI, percutaneous coronary intervention; pts, patients; RCTs, randomized controlled trials; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in myocardial infarction.

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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.eurorocrates.com] were also considered. The following keywords were applied: “adenosine”; “acutecoronarysyndrome”; “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 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 (12) $\left(\frac{Q}{df}\right) / Q \times 100\%$, 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 [10–15,16–18], involving 3821 patients, met the inclusion criteria and were included in the meta-analysis (Fig. 1).
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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal (year)</th>
<th>Adenosine + placebo pts</th>
<th>Follow-up time (months)</th>
<th>Setting</th>
<th>Route of adenosine</th>
<th>Dose of adenosine</th>
<th>Treatment strategy</th>
<th>Ischemic time before treatment (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMISTAD-I [10]</td>
<td>JACC (1999)</td>
<td>236</td>
<td>1.4</td>
<td>STEMI</td>
<td>IV</td>
<td>70 μg/kg/min for 3 h</td>
<td>Thrombolysis</td>
<td>111</td>
</tr>
<tr>
<td>ATTACC [12]</td>
<td>Eur J Clin Pharmacol</td>
<td>608</td>
<td>12</td>
<td>STEMI</td>
<td>IV</td>
<td>10 μg/kg/min for 6 h</td>
<td>Thrombolysis</td>
<td>208</td>
</tr>
<tr>
<td>Fokkema [14]</td>
<td>Circ Cardiovasc Interv</td>
<td>448</td>
<td>1</td>
<td>STEMI</td>
<td>IC</td>
<td>2 × 120 μg in 20 mL 0.9% NaCl</td>
<td>PCI</td>
<td>180</td>
</tr>
<tr>
<td>Grygier [15]</td>
<td>Am J Cardiol (2011)</td>
<td>70</td>
<td>1</td>
<td>STEMI</td>
<td>IC</td>
<td>2 mg to the left artery, 1 mg to the right artery in ~1 min</td>
<td>PCI</td>
<td>270</td>
</tr>
<tr>
<td>Marzilli [16]</td>
<td>Circulation (2000)</td>
<td>54</td>
<td>In-hospital</td>
<td>STEMI</td>
<td>IC</td>
<td>4 mg in ~1 min</td>
<td>PCI</td>
<td>106</td>
</tr>
<tr>
<td>Tian [17]</td>
<td>Chinese Medical J (2008)</td>
<td>26</td>
<td>1</td>
<td>STEMI</td>
<td>IC</td>
<td>2 mg/min for 10 min</td>
<td>PCI</td>
<td>na</td>
</tr>
</tbody>
</table>
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], $p = 0.01$.

---

**Mortality**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>adenosine Events</th>
<th>placebo Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMISTAD I</td>
<td>10</td>
<td>8</td>
<td>18</td>
<td>3.7%</td>
<td>1.70 [0.80, 3.63]</td>
<td></td>
</tr>
<tr>
<td>AMISTAD II</td>
<td>146</td>
<td>144</td>
<td>290</td>
<td>65.7%</td>
<td>0.86 [0.58, 1.29]</td>
<td></td>
</tr>
<tr>
<td>ATTACC</td>
<td>32</td>
<td>302</td>
<td>334</td>
<td>22.9%</td>
<td>0.81 [0.49, 1.33]</td>
<td></td>
</tr>
<tr>
<td>Desmet</td>
<td>2</td>
<td>56</td>
<td>58</td>
<td>1.3%</td>
<td>0.98 [0.13, 7.09]</td>
<td></td>
</tr>
<tr>
<td>Fokkema</td>
<td>3</td>
<td>226</td>
<td>229</td>
<td>1.3%</td>
<td>1.40 [0.24, 8.94]</td>
<td></td>
</tr>
<tr>
<td>Grygier</td>
<td>0</td>
<td>35</td>
<td>35</td>
<td>2.3%</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Marzilli</td>
<td>0</td>
<td>27</td>
<td>27</td>
<td>0.5%</td>
<td>0.07 [0.00, 1.42]</td>
<td></td>
</tr>
<tr>
<td>Stoel</td>
<td>3</td>
<td>27</td>
<td>30</td>
<td>0.5%</td>
<td>2.63 [0.25, 27.19]</td>
<td></td>
</tr>
<tr>
<td>Vijayalakshmi</td>
<td>0</td>
<td>51</td>
<td>51</td>
<td>1.3%</td>
<td>0.32 [0.01, 8.05]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>2257</td>
<td>1536</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>196</td>
<td>139</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 5.90$, df = 7 ($p = 0.65$); $I^2 = 0$%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 1.20$ ($p = 0.23$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**No-reflow**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>adenosine Events</th>
<th>placebo Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMISTAD I</td>
<td>0</td>
<td>7</td>
<td>7</td>
<td>100%</td>
<td>0.07 [0.00, 1.29]</td>
<td></td>
</tr>
<tr>
<td>Fokkema</td>
<td>2</td>
<td>226</td>
<td>228</td>
<td>6.3%</td>
<td>1.97 [0.18, 21.92]</td>
<td></td>
</tr>
<tr>
<td>Marzilli</td>
<td>1</td>
<td>27</td>
<td>28</td>
<td>42.7%</td>
<td>0.11 [0.01, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Tian</td>
<td>0</td>
<td>12</td>
<td>12</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vijayalakshmi</td>
<td>0</td>
<td>51</td>
<td>51</td>
<td>9.5%</td>
<td>0.32 [0.01, 8.05]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>435</td>
<td>430</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>3</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 4.16$, df = 3 ($p = 0.24$); $I^2 = 28$%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.59$ ($p = 0.010$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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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.
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.)
3.3.4. ST-segment resolution

Four studies reported the incidence of $\geq$50% ST-segment resolution after intracoronary adenosine vs. placebo. Patients treated with intracoronary adenosine showed a non-significant trend towards greater ST-segment resolution compared to the patients in the placebo group: 62.5% (215/344) vs. 52.9% (186/353), OR$_{\text{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 $\geq$ 6 months ($p$ for interaction = 0.79); (3) studies enrolling a total number of patients $>101$ or $\leq 101$ 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 antiarrhythm 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 ischemia 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, surrogates 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) (cf. 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