Platelet glycoprotein IIb/IIIa blockers during percutaneous coronary intervention and as the initial medical treatment of non-ST segment elevation acute coronary syndromes (9819)

Review information

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What's new

Date	Event	Description
12 July 2010	Updated	Change in authors.
12 July 2010	New citation: conclusions changed	In the current version we have added 10 new studies in the PCI group, five performed during primary PCI in patients with ST-segment elevation acute myocardial infarction, four in patients with stable coronary artery disease and one in a mixed population. Four of these 10 studies were performed in patients pre-treated with clopidogrel. No new studies have been added to the group of patients with non-ST segment elevation acute coronary syndromes in which IIb/IIIa blockers were given as initial medical treatment. However, two studies that were previously analysed in the PCI group based on preliminary data from congress reports have been finally included in this group. Conclusions about IIb/IIIa blockers during PCI have slightly changed to include reduction in six month mortality for the overall group, and also to underline that the results are homogeneous for all the subgroups that have been analysed except for patients pretreated with clopidogrel where these drugs seem to be effective only in patients with an Acute Coronary Syndrome. Conclusions about IIb/IIIa blockers as initial treatment of NSTEACS are unchanged.

History

Date	Event	Description
9 September 2008	Amended	Converted to new review format
22 December 2006	New citation: conclusions changed	Substantive amendment

Abstract

Background

During percutaneous coronary intervention (PCI), and in non-ST segment elevation acute coronary syndromes (NSTEACS), the risk of acute vessel occlusion by thrombosis is high. IIb/IIIa blockers strongly inhibit platelet aggregation and may prevent mortality and myocardial infarction (MI). This is an update of a Cochrane review first published in 2001, and previously updated in 2007.

Objectives

To assess the effects and safety of IIb/IIIa blockers when administered during PCI, and as initial medical treatment in patients with NSTEACS.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (Issue 3, 2009), MEDLINE (1966 to October 2009), and EMBASE (1980 to October 2009).

Selection criteria

Randomised controlled trials comparing intravenous IIb/IIIa blockers with placebo or usual care.

Data collection and analysis

Two authors independently selected studies for inclusion, assessed trial quality and extracted data. We collected major bleeding as adverse effect information from the trials. Odds ratios (OR) and 95% confidence intervals (CI) were used for effect measures.

Main results

Forty-eight trials involving 62,417 patients were included. During PCI, IIb/IIIa blockers decreased mortality at 30

days (OR 0.76, 95% CI 0.62 to 0.95) and at six months (OR 0.84, 95% CI 0.71 to 1.00). Death or MI was decreased both at 30 days (OR 0.65, 95% CI 0.60 to 0.72), and at 6 months (OR 0.70, 95% CI 0.61 to 0.81), although severe bleeding was increased (OR 1.38, 95% CI 1.20 to 1.59; absolute risk increase (ARI) 8.0 per 1000). The efficacy results were homogeneous for every endpoint according to the clinical condition of the patients, but were less marked for patients pre-treated with clopidogrel, especially in patients without ACS.

As initial medical treatment of NSTEACS, IIb/IIIa blockers did not decrease mortality at 30 days (OR 0.91, 95% CI 0.80 to 1.03) or at six months (OR 1.00, 95% CI 0.87 to 1.15), but slightly decreased death or MI at 30 days (OR 0.92, 95% CI 0.86 to 0.99) and at six months (OR 0.88, 95% CI 0.81 to 0.96), although severe bleeding was increased (OR 1.27, 95% CI 1.12 to 1.43; ARI 1.4 per 1000).

Authors' conclusions

When administered during PCI, intravenous IIb/IIIa blockers reduce the risk of death and of death or MI at 30 days and at six months, at a price of an increase in the risk of severe bleeding. The efficacy effects are homogeneous but are less marked in patients pre-treated with clopidogrel where they seem to be effective only in patients with ACS. When administered as initial medical treatment in patients with NSTEACS, these agents do not reduce mortality although they slightly reduce the risk of death or MI.

Plain language summary

Platelet glycoprotein IIb/IIIa blockers during percutaneous coronary intervention and as the initial treatment of non-ST segment elevation acute coronary syndromes

During the last two decades, doctors have been looking for the best treatment to prevent clots in the coronary arteries of patients with coronary heart disease. This review summarises the results of 48 studies which used a potent class of intravenous antiplatelet drug - glycoprotein IIb-IIIa blockers. This treatment was tested in two different conditions: in patients undergoing percutaneous coronary intervention (PCI) procedures (coronary angioplasty with or without stenting), and as the initial treatment of patients hospitalised for acute coronary syndromes (unstable angina and non-ST segment elevation acute myocardial infarction).

Overall, the use of these drugs during PCI reduced the risk of death and of death or myocardial infarction at 30 days and at 6 months. The results were similar for stable and for unstable patients with coronary artery disease, but there was comparatively less benefit for patients previously treated with clopidogrel, a new oral antiplatelet drug. However, these drugs only slightly reduced the risk of death or myocardial infarction when administered as initial medical treatment in patients with unstable angina or non-ST-elevation myocardial infarction. The benefits of glycoprotein IIb/IIIa blockers need to be balanced against the increased risk of severe bleeding.

Background

Description of the condition

Cardiovascular diseases were the direct cause of > 4 million deaths in Europe around the year 2000 (1.9 million in the European Union), accounting for 43% of all deaths of all ages in men and 55% in women. Coronary artery disease (CAD) accounts for half of this mortality burden and depends mostly on the occurrence of acute coronary syndromes (ACS). (ESC Prevention Guidelines 2007).

According to the current European and American guidelines, most of the patients with an ACS should be referred for coronary angiography, as they recommend percutaneous coronary intervention (PCI) as the preferred treatment option for both patients with ST-segment elevation myocardial infarction (MI), patients with non-ST elevation MI, and also in high-risk patients with unstable angina (ACC/AHA 2007; ESC 2007). In addition, PCI is the preferred revascularization technique for patients with stable CAD. As a consequence, the number of PCI procedures are rapidly increasing.

Description of the intervention

The mechanism of PCI using balloon angioplasty with or without stent implantation, includes profound vessel injury and plaque rupture, all of which triggers an immediate activation of the coagulation cascade, and adhesion, activation, and aggregation of platelets (ACC/AHA 2007; ESC 2007). Pre-treatment with aspirin, ticlopidine and heparin has been shown to reduce by 70% the risk of acute vessel occlusion and of myocardial infarction in these patients (ATC 2002). Bivalirudin, a new anticoagulant drug that is a direct thrombin inhibitor, has also shown to have similar efficacy than unfractionated heparin with less bleeding (ACUITY 2006; HORIZONS-AMI 2008). When a stent is implanted, the addition of clopidogrel before the procedure and during follow-up has also shown to be of benefit (PCI-CURE 2001). Thus, treatment with aspirin, clopidogrel and heparin or bivalirudin is the standard antithrombotic treatment for this procedure (ACC/AHA 2007; ESC 2007).

The pathophysiology of non-ST segment elevation ACS (NSTEACS), i.e. unstable angina and non-ST segment elevation myocardial infarction, involves the rupture or erosion of an atherosclerotic coronary plaque (Falk 1995), activation of the coagulation cascade, and adhesion, activation, and platelet aggregation. Treatment with aspirin and fractionated or unfractionated heparin has been shown to reduce the risk of cardiac events by 50% in patients with this syndrome (ATC 2002; Mehta 2003). The addition of clopidogrel has also shown to further decrease the risk of vascular events by 20% in these patients (CURE 2001). Finally, fondaparinux, a new anticoagulant, has shown to have similar efficacy with less bleeding effects than heparin (OASIS-5 2006). Thus,

the current standard antithrombotic treatment for patients with NSTEACS is the administration of aspirin and clopidogrel with heparin or fondaparinux as recommended in current clinical guidelines (ESC 2007; ACC/AHA 2007).

The glycoprotein (GP) IIb/IIIa integrin present in platelets mediates the final common pathway in platelet aggregation, spawning the development of GP IIb/IIIa receptor blockers (Phillips 1988). Intravenous GP IIb/IIIa inhibitors block up to 80% of the GP IIb/IIIa platelet receptors (Gurbel 2005).

How the intervention might work

In patients with NSTEACS, and also in patients submitted to PCI, intravenous GP IIb/IIIa blockade induce strong platelet inhibition (Gurbel 2005) and may prevent mural and intraluminal thrombus formation that can result in the prevention of both acute coronary occlusion and of embolization of plaque thrombi to the distal microvasculature resulting in MI (Boersma 1999).

Why it is important to do this review

In spite of their known effects in preventing MI, some doubts remain on the efficacy of these drugs in decreasing mortality, the homogeneity of their effects in different subgroup of patients or PCI techniques used, and on their additional benefit when patients are pretreated with clopidogrel. In addition, since GP IIb/IIIa receptor blockers induce profound platelet inhibition, the risk of bleeding complications is increased, particularly when administered concomitantly with other antiplatelet drugs and with high-dose heparin treatment (Quinn 2002). Thus, safety is an important issue in the management of patients with these drugs, especially during PCI.

This is an update of a Cochrane review first published in year 2001, and previously updated in year 2007. In the last update, the main conclusion was that when administered during PCI, IIb/IIIa blockers reduced the risk of death at 30 days but not at six months, and of death or MI at 30 days and six months. In contrast, when administered as initial medical treatment in patients with NSTEACS, these drugs do not reduce mortality, slightly reduce the risk of death or MI, and increase the risk of severe bleeding.

In the last three years, several studies have been performed with these drugs in the setting of PCI (3T/2R 2009; BRAVE-3 2009; CLEAR PLATELETS-2 2009; Cuisset 2008; Fu 2008; JEPPORT 2009; On-TIME 2 2008; OPTIMIZE-IT 2009; Shen 2008). In addition, new oral antiplatelet (i.e. clopidogrel) (CURE 2001, PCI-CURE 2001) and anticoagulant (i.e. bivalirudin and fondaparinux, ACUITY 2006, HORIZONS-AMI 2008, OASIS-5 2006) drugs have been incorporated in the usual medical treatment of the patients with acute coronary syndromes and in patients referred for PCI (ACC/AHA 2007; ESC 2007). Since the efficacy and bleeding risk of the intravenous IIb/IIIa blockers could be different in the presence of these new drugs, an update of this systematic review seems to be justified.

Objectives

The aim of this systematic review was to assess the effectiveness of GP IIb/IIIa blockers given in addition to standard medical treatment when administered:
1. During PCI.
2. As the initial medical treatment of patients with NSTEACS ("upstream treatment").

The first indication relates to a procedure rather than a health problem and the studied treatment was administered a few minutes prior PCI. The second relates to a clinical condition that includes a wide range of patient groups at different risk, and the studied treatment was administered at admission in patients with or without coronary angiography and PCI during hospitalisation.
The standard medical treatment considered was aspirin and ticlopidine or clopidogrel, plus heparin or bivalirudin during PCI; and aspirin with or without clopidogrel, and heparin or fondaparinux in the initial medical treatment of patients with NSTEACS.

Methods

Criteria for considering studies for this review

Types of studies

We sought to identify all randomised controlled clinical trials, with or without blinding, studying intravenous GP IIb/IIIa blockers and in which at least one of the pre-defined primary outcomes was measured. Specifically, we analysed trials performed when IIb/IIIa blockers were administered during PCI in patients with or without an ACS, and trials performed in patients with NSTEACS treated from admission with GP IIb/IIIa antagonists as the initial medical management.

We did not consider trials:

- On oral GP IIb/IIIa blockers, since clinical research has indicated that their administration is associated with increased mortality.
- Performed in patients with ST-segment elevation acute myocardial infarction (STEMI) treated with thrombolytics or with facilitated or rescue PCI after thrombolytic treatment.
- In which the timing of the GP IIb/IIIa blockers administration was analysed (i.e. comparing pre-hospital administration vs. hospital administration or administration in the emergency room vs. in the catheterization laboratory).

Types of participants

The following participants were considered for each of the two types of studies that we considered in this review:

1. Studies that randomised adults (18 years and older) male or female with or without an acute coronary syndrome that underwent PCI.

These studies were performed in stable or unstable coronary patients undergoing elective or urgent PCI with or without stent implantation, and IIb/IIIa blockers were administered during the procedure. In all the studies performed during elective PCI, randomisation was performed when the exact coronary anatomy was known and inclusion criteria required the presence of one or more > 70% stenosis in a coronary segment amenable to PCI. Most of the studies excluded patients with renal dysfunction and those at risk of bleeding.

2. Studies that included adult patients with NSTEACS in which GP IIb/IIIa antagonists were administered at the time of hospital admission as part of the initial medical management.

These studies were performed in patients with a recent (< 24 hs) chest pain associated with ischaemic changes in the admission ECG (ST-segment depression >0.5 mm or transient elevation > 1mm, > 1mm T-wave inversion) or CK-MB or troponin elevation above the upper limits of normality in each participant institution. Most of these trials were performed in patients managed conservatively except for ELISA-2 2006, PRISM Plus 1998 and PRACTICE 2007.
All of the studies excluded patients with moderate to severe renal dysfunction and those at risk of bleeding.

Types of interventions

Intravenous GP IIb/IIIa blockers administered as a bolus followed by 12 to 96 hours infusion, at any dose, compared with a control group with or without placebo, on top of usual care (aspirin and ticlopidine or clopidogrel, and heparin or bivalirudin).

Three GP IIb/IIIa blockers parenterally administered during PCI (abciximab, eptifibatide and tirofiban) and four administered in the initial management of patients with NSTEACS (abciximab, eptifibatide, lamifiban and tirofiban) have been tested.

Comparators

For every major endpoint, two subgroup analyses have been performed:

1. PCI Group
   - GP IIb/IIIa blockers compared with placebo (double blind studies) on top of usual care
   - GP IIb/IIIa blockers compared with usual care
2. Initial medical treatment of patients with NSTEACS
   - Since only one small study did not include a blinded placebo group, no subgroup analysis were performed for this indication.

Types of outcome measures

Primary outcomes

- All-cause mortality at 30 days and six months.
- Death or non-fatal myocardial infarction at 30 days and six months.

The combined endpoint of death or myocardial infarction was chosen because most deaths (all-cause mortality) occurring early after a NSTEACS or a PCI procedure are due to an acute coronary occlusion leading to a myocardial infarction.

Because definitions of myocardial infarction may vary among studies specially in those performed during PCI, when de data was obtainable we used as a definition of post-procedural MI an elevation >3 times the upper limit of normal of the used biomarker of necrosis (creatinine kinase-MB fraction (CK-MB) or cardiac troponins).

Secondary outcomes

- Need for an urgent revascularisation procedure at 30 days and six months for patients who underwent PCI.

Urgent revascularisation was chosen as a secondary endpoint since this is a consequence of refractory ischaemia and since its indication is often clinician-driven and, in consequence, not entirely objective.

- Death, non-fatal MI or urgent coronary revascularisation at 30 days and six months.

This endpoint was combined with death and myocardial infarction because all share the same pathophysiology (i.e. acute vessel occlusion) also as a secondary endpoint.

- Safety: severe bleeding at 30 days.

This was the most important safety outcome that was appropriately described in all studies. Wherever reported the Thrombolysis In Myocardial Infarction (TIMI) classification was used to define severe bleeding (Bovill 1991); the investigator's definition was used otherwise.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (Issue 3, 2009), MEDLINE (1966 to October 2009), and EMBASE (1980 to October 2009). Search strategies were checked and revised for the updates. See Appendix 1; Appendix 2; and Appendix 3 for details of the search strategies. All records were loaded into Reference Manager and duplicates removed (see Acknowledgements).

Searching other resources

Handsearches were done (to October 2009) of abstracts from conferences published in *Circulation* (American Heart Association Annual Meeting), *Journal of the American College of Cardiology* (American College of Cardiology Annual Congress), *American Heart Journal, European Heart Journal* (European Society of Cardiology Annual Congress), *Revista Española de Cardiologia*, and online at Theheart.org, TIMI.org, and Clinicaltrials.org. The references sections of reviews addressing GP IIb/IIIa inhibitors were also examined.

No language restrictions were applied to the search. English, French and Spanish language papers were read by the authors. The Cochrane Heart group helped us by translating one Chinese article (see Acknowledgements). Only one published study could not be retrieved from the bibliographic search (Gasior 2003).

Data collection and analysis

Selection of studies

Results were screened and extracted independently by two authors. A paper was rejected only when both reviewers agreed that the article did not meet the inclusion criteria. Each manuscript was scored independently by two reviewers using a pre-designed in/out form. Each manuscript was scored 1 (definitely "in", i.e. the study met the inclusion criteria); 2 (maybe in, i.e. small sample size or difficult to determine the type of control or of diagnosis); or 3 (definitely out, i.e. definitely did not meet the inclusion criteria). All manuscripts which scored at least one "1" or one "2" were analysed in common by both reviewers.

Data extraction and management

Two authors independently extracted data from original reports of trial results, and differences were resolved by discussion. Data on characteristics of participants (age, sex, presence of diabetes, prior myocardial infarction, ACS and type), interventions (PCI and type, stent and type, pretreatment with clopidogrel), outcomes, trial quality characteristics (i.e. sequence generation, allocation concealment, blinding, incomplete outcome report, incomplete data addressing, selective reporting and other) were abstracted onto this form. In addition, data were collected on potential confounding factors including participants' baseline risk and characteristics, trial duration, intensity of intervention (dosing and duration of treatment), type and dose of concomitant medication used and revascularization procedures including stent implantation.

Assessment of risk of bias in included studies

Two authors independently assessed risk of bias in the included studies using the Cochrane Collaboration's risk of bias tools (Higgins 2008). A risk of bias table for each study was created by adding the degree of bias for the primary and secondary endpoints according to sequence generation, allocation concealment, blinding, incomplete outcome report, incomplete data addressing, selective reporting and other.

In addition, the risk of bias was further analysed by including two tables with the summary assessment of the risk of bias for major and minor endpoints (across key domains) within and across studies. Allocation concealment and blinding were selected as the key domains for this analysis.

Data synthesis

Heterogeneity of studies was assessed by clinical judgement according to differences in type of patients enrolled, study quality, interventions and outcome. Pooled odds ratio (OR) of the individual and combined endpoints were calculated. Fixed-effect meta-analyses are presented unless a chi-squared test for heterogeneity was statistically significant at a 5% level, in which case random-effects meta-analyses are presented. Risk differences were calculated after pooling together the studies for each meta-analysis.

Subgroup analysis and investigation of heterogeneity

In the analysis of the effects of GP IIb/IIIa blockers administered during PCI, six separate subgroup analysis were performed:

1. According to the clinical condition of the patients:

- Stable coronary artery disease in which PCI was performed as an elective procedure.
- NSTEACS
- Primary PCI in patients with STEMI

2.The technique used:

- Balloon angioplasty alone
- PCI with stent implantation

3. Pretreatment with clopidogrel.

- Patients with ACS
- Patients without ACS

For all subgroup analyses we selected studies in which at least two thirds of patients had the focused condition or procedure. For the analysis of patients pre-treated with clopidogrel and according to the known dose-related onset of action of this drug (Hochholzer 2005), we selected only trials in which patients were receiving chronic clopidogrel treatment or a loading dose of 300 mg was administered ≥6 hs before the procedure, or a loading dose ≥450 mg was administered ≥2 hours before the procedure or at the time of randomisation for patients with STEMI planned for primary PCI.

No subgroup analyses were performed in the group of IIb/IIIa blockers administered as initial medical treatment in patients with NSTEACS.

Only the effect of the intravenous route of administration (i.e. bolus plus infusion) was examined and compared with placebo/control with usual care (i.e. aspirin, ticlopidine/clopidogrel, and heparin/bivalirudin). To prevent attrition bias, all patients allocated to active treatment were analysed in this group regardless of whether they received it or not (i.e. intention-to-treat analysis). Intention-to-treat data were used in the pooled analyses of this review as it was possible to obtain them from the publications of all the studies.

Sensitivity analysis

In the PCI meta-analysis, two different analysis were made in the overall group according to the presence or absence of a high risk of bias for the primary endpoint of the review. Group 1, studies at low to intermediate risk of bias (i.e. Comparison with placebo, double-blind and with adequate allocation concealment); and Group 2, studies at high risk of bias (i.e. comparison with usual care, without placebo and not blinded). A sensitivity analysis was made by comparing the results for each group and for the two groups together.

Results

Description of studies

Results of the search

The search strategy was designed to be very sensitive and yielded 3,336 documents from the original, and the 2007 and 2010 updates of the review. All references from relevant reviews and meta-analyses (see "other references") were screened for studies possibly missed by our search strategy, however no additional studies were identified. In total 164 articles were retrieved for further examination, 42 of these were from the current update. Ninty four references to 92 studies were excluded (see Characteristics of excluded studies) and one paper was unobtainable and we were unable to assess for inclusion (Gasior 2003). Ten new RCTs were identified from the current update. The previous version of the review included 38 RCTs so that in total 48 trials (62,417 participants), reported in 69 articles were included in the review. Of these 38 trials were on GP IIb/IIIa blockers administered during PCI and 10 trials tested these drugs as initial medical treatment in patients with NSTEACS. See QUOROM statement for details (Figure 1).

Included studies

Almost all of the studies were multicenter, international studies and were performed mostly in North America and Europe, specially in the United States, Canada, The Netherlands, France, Belgium, Germany, Spain, Poland and Italy. An important number were also performed in south American countries, Australia, New Zealand and the Czech Republic.

Most of the included studies came out before clopidogrel was available.

During percutaneous coronary intervention

PCI was the condition studied in 38 studies with 31,020 patients. Thirty-six studies reported outcomes at 30 days while 23 studies reported outcomes at 6 months.
Among the 38 studies and according to the clinical condition of the patients, there were 13 studies in patients with stable CAD, 4 studies in patients with NSTEACS, and 10 studies performed during primary PCI in patients with ST-segment elevation myocardial infarction (STEMI); the other 11 studies were performed in a mixed population. According to the technique used, there were 11 studies performed during balloon angioplasty, 24 during PCI with stent and three with mixed techniques. Finally, 11 studies were performed in patients pre-treated with clopidogrel, five in patients with ACS and six in patients without ACS.

All patients included in trials with stent implantation received heparin, aspirin and ticlopidine or clopidogrel during and after the procedure except for the ERASER 1999 study in which ticlopidine was left to the investigator's discretion. No study was performed specifically in patients in which a drug-eluting stent was implanted, and in only three studies (BRAVE-3 2009; CLEAR PLATELETS-2 2009; ISAR-REACT 2 2006; OPTIMIZE-IT 2009) a drug-eluting stent was used in 40% to 72% of the cases. Abciximab was used in 19 trials, tirofiban in six, and eptifibatide in four. The doses varied among studies.

As initial medical treatment of patients with non-ST segment elevation acute coronary syndromes

Ten studies with 31,069 patients concerned GP IIb/IIIa use as initial medical treatment in patients with NSTEACS. All these studies presented 30-day follow-up results and four that of six months. Abciximab was used in one study, eptifibatide in three, tirofiban in three, and lamifiban in three.

PRISM 1998 differed from the other trials in that the GP IIb/IIIa blocker was given without heparin. PRISM Plus 1998 also initially contained an arm with GP IIb/IIIa blocker without heparin. The PARAGON A 1998 study also included an arm without heparin. Seven studies were performed following a conservative management while only three (ELISA-2 2006, PRACTICE 2007 and PRISM Plus 1998) were performed on an invasive basis with most of the patients scheduled for early coronary angiography.

Variability

The potential sources of heterogeneity among the studies may include the variability in patient characteristics. In the PCI group the mean age ranged from 59 years to 70 years with a median of 61 ys, while in the group of studies on initial medical treatment of NSTEACS the mean age ranged form 60 to 65 ys. Considering all studies, the proportion of males ranged from 61% to 95%, and the proportion of patients with prior myocardial infarction, which was described in most studies, ranged from 10% to 67% (see characteristics of included studies table).

In the PCI analysis, 10 trials were performed in patients with STEMI, nine of them during primary PCI. The frequency of this diagnosis was of 0% in 22 other studies and ranged from 3% to 41% in the other 4 trials. A specific analysis of those 9 trials has been performed.

In the analysis of GP IIb/IIIa blockers administered as initial medical treatment in patients with NSTEACS, the prevalence of unstable angina ranged from 43% to 86%, and that of non-ST-segment elevation myocardial infarction from 14% to 100%. Thirty-two to 80% of patients had ST-segment depression at enrolment. Seven studies were performed following a conservative management with less than 14% of patients having in-hospital PCI. In the other 3 studies, coronary angiography was performed in 60% to 90% of patients, and PCI from 31% to 61% of patients during drug infusion which was administered for 24 to 72 hours after enrolment.

The daily doses of aspirin ranged in the studies from 50 mg to 500 mg and those of heparin were typically aimed at maintaining an activated clotting time >200 seconds or an activated partial thromboplastin time between 50 and 85 seconds, or twice that of laboratory control. Only in one study (Schulman 1996) was aspirin not allowed in the treatment group but administered in the placebo group.

Some studies had arms of active treatment with lower heparin doses (EPILOG 1997) or no heparin at all (PARAGON A 1998; PRISM Plus 1998; PRISM 1998). All patients of these studies were included in the present update since a prior meta-analysis performed with individual patient data reported similar results by including or excluding those patients (Boersma 2002). Patients of the control groups of all studies received heparin.

Dosing

Where trials had intervention arms with varying doses of GP IIb/IIIa inhibitor drugs, data from such intervention arms were pooled. In the EPIC 1994 study, one intervention arm had GP IIb/IIIa blocker administered as a bolus alone, i.e. with no subsequent perfusion; the results of that arm were not included.

Endpoints

Three studies describing endpoints occurring within follow-up periods shorter than 30 days (i.e. in-hospital, 7-day, etc..) were pooled with 30-day follow-up studies (ERASER 1999; Kereiakes 1996; Simoons 1994) due to the fact that most of adverse events occur within the first week after the event or the procedure. Also, one study (ADVANCE 2004) that only reported events at six months was also included in the 30-day follow-up analysis in order not to miss this important information considering that >80% of mortality and myocardial infarction and >95% of severe bleeding occurred during the first 30 days. Finally, three studies (ISAR-REACT 2004; ISAR-REACT 2 2006; ISAR-SMART-2 2004) that reported the 1-year follow-up alone were pooled with the 6-month follow-up analysis for the same reason.

Definitions about Myocardial infarction varied widely among studies specially in those performed during PCI. Whan de data was obtainable we used as a definition of post-procedural MI an elevation >3 times the upper limit of normal of the used biomarker of necrosis (Ck-MB or Troponins).

In some instances, the nature of PCI during follow up was not specified to be urgent or not. In such cases, overall revascularizations were considered.

Excluded studies

Most of the excluded studies did so because they were not RCT's, did not reported clinical events, or were performed in conditions other than during PCI or as initial medical treatment of patients with NSTEACS (Figure 1)

Risk of bias in included studies

It is important to note that most of the trials excluded patients at high risk of bleeding and patients with renal failure. In addition, the mean age of the studied population was lower (61 years) than what it is usually observed in clinical practice (CRUSADE 2006, GRACE 2007).

The definition of primary and secondary outcomes varied among studies. However, it was possible to obtain or calculate the number of cases with the primary and secondary endpoints of this review in most studies. We chose to combine death or non-fatal myocardial infarction because most deaths (all cause mortality) occurring early after NSTEACS or PCI are due to myocardial infarction and both events share the same pathophysiology, i.e. acute coronary vessel occlusion or distal coronary embolization.

Myocardial infarction was part of the composite effectiveness endpoint of all trials, but the applied myocardial infarction definition was different especially regarding the required level of increased levels of the MB fraction of creatine kinase in studies performed before year 2005 and of troponin levels thereafter. This point was specially important regarding the definition of post-PCI myocardial infarction. Because of this, and when de data was obtainable, we used as a definition of post-procedural MI an elevation >3 times the upper limit of normal of the used biomarker of necrosis (creatinine kinase-MB fraction (CK-MB) or cardiac troponins).

The secondary endpoint 'major bleeding', was assessed by the Thrombolysis In Myocardial Infarction (TIMI) classification when described (bleeding was classified as major if it involved intracranial haemorrhage or cardiac tamponade or if it was associated with a decrease in haemoglobin concentration of more than 50 g/L regardless of whether or not a bleeding site had been identified (Bovill 1991). Otherwise, the 'major' bleeding described in each study was used. When no description of major bleeding existed at all, brain haemorrhages and need for transfusion were selected as 'major' bleeding.

All studies followed more than 95% of patients at 30 days and more than 90% at six months.

In general the methodological quality of the 48 selected randomised controlled trials was good, but differed in PCI and non-PCI studies. Ten of the 38 PCI trials were considered to be at high risk of bias (Table 1). However, these 10 studies included only 3863 patients (12.45% of the total patients) and had been studied separately on this review for each major endpoint. In contrast, among studies on IIb/IIIa blockers administered as initial medical treatment in patients with NSTEACS, only one small study (ELISA-2 2006) was considered as a high risk of bias (Table 2)

Allocation

Adequate sequence generation was obtained in 83% of the studies and adequate allocation concealment in 64% of them. Only in 10% of the studies the allocation concealment was inadequate (or considered to be at high risk of bias (Figure 2; Figure 3).

Blinding

Patients and clinicians were adequately blinded to treatment in most of the trials. Some studies were performed in an open-label basis while in others (Claeys 2005 and ISAR-2 2000) the treatment strategy precluded blinding of the used drugs. Overall, for the primary endpoint of the review, blinding of patients and investigators was adequate in 64% of the studies, unclear in 8% and inadequate in 28% of them. For the secondary endpoints, blinding was adequate in 57%, unclear in 12% and inadequate in 31% (Figure 2; Figure 3).

Regarding allocation concealment and blinding as the two major key domains, the risk of bias across PCI studies was low for mortality and unclear for death or MI, and for major bleeding (Table 1). In studies performed with the use of IIb/IIIa blockers as initial medical treatment in patients with NSTEACS, the risk of bias across studies was low for every major endpoint (Table 2).

Incomplete outcome data

Incomplete outcome data on the primary endpoint was adequately addressed in 94% of the studies and on the secondary endpoints in 92% of them (Figure 2; Figure 3)

Selective reporting

Ninety-four percent of the studies were free of suggestion of selective outcome reporting (Figure 2).

Other potential sources of bias

Almost all studies were industry funded, enhancing the risk of bias (Als-Nielsen 2003). In fact, only 20% of them were apparently free of other problems that could put it at a risk of bias. Fifty-six percent of the studies were considered as an unclear risk of bias and 24% were at high risk because of investigators and industry relationship or premature stop of the study (Figure 2; Figure 3).

Effects of interventions

1. GP IIb/IIIa blockers during percutaneous coronary intervention

Primary endpoints

of the 38 PCI trials with 31,020 patients, data from 36 trials with 30,696 patients (99% of patients included in this meta-analysis) were available on 30-day mortality, and mortality or myocardial infarction. Twenty-six of these trials with 26,833 patients (87%) were blinded studies with a placebo group and considered to be at low risk of bias. Six-month data on mortality and on mortality or myocardial infarction was available from 24 trials with 22,364 patients (72%), of which 17 trials (19,157 patients) were blinded and at low risk of bias Table 1.

Mortality

Mortality occurred in 0.91% of patients in the treatment group versus 1.32% in controls at 30 days, and in 2.30% and 2.93% respectively at six months. Treatment with intravenous GP IIb/IIIa blockers was associated with a significant reduction in the odds of mortality at 30 days (OR 0.76, 95% CI 0.62 to 0.95, P = 0.01). The results were homogeneous (I^2=0%) and similar for blinded (0.78, 95% CI 0.61 to 1.00) and unblinded studies (0.72, 95% CI 0.47 to 1.12). Please refer to Analysis 1.1 and Figure 4. The absolute risk reduction (ARR) per thousand treated

patients was of 4.1 (95% CI 1.7 to 6.5) and the number needed to treat (NNT) to save a life of 244. The results were also similar for all the different subgroups that were considered according to the clinical condition of the patients (Analysis 2.1; Analysis 3.1; Analysis 4.1) and the technique used (Analysis 5.1; Analysis 6.1), although they were less marked for patients pre-treated with clopidogrel (OR 0.83, 95% CI 0.56 to 1.22; Analysis 7.1; Table 3).

However, at six months the initial benefit was less marked in the overall group (OR 0.84, 95% CI 0.71 to 1.00, P = 0.04; I^2=0%; Analysis 1.2; Figure 5), and in each subgroup except for patients with STEMI treated during primary PCI (OR 0.72, 95% CI 0.53 to 0.99; Table 3). The ARR per thousand treated patients in the overall group was of 6.3 (95% CI 2.1 to 10.5) and the NNT of 160.

Death or MI

The rate of death or MI at 30 days and six months was of 5.10% vs. 7.52% and 7.51% vs. 10.45% in the treatment and control groups respectively. GP IIb/IIIa blockers were also associated with a significant decrease in the odds of death or MI at 30 days (OR 0.65, 95% CI 0.60 to 0.72, P<0.00001; I^2=25%) without significant differences between blinded and unblinded studies (Analysis 1.3; Figure 6). The ARR per thousand treated patients was of 24.2 (95% CI 18.7 to 29.8) and the NNT of 42. The results were similar in all subgroups but were less marked in patients pretreated with clopidogrel (OR 0.80, 95% CI 0.66 to 0.96), especially in patients without ACS (OR 0.97, 95% CI 0.70 to 1.35; Analysis 7.3; Table 3).

The results at six months showed marked heterogeneity (I^2=43%) but were similar to those obtained at 30 days (OR 0.70, 95% CI 0.61 to 0.81, P<0.00001; Analysis 1.4). The ARR per thousand treated patients was of 29.4 (95% CI 22.0 to 36.9) and the NNT of 34. Again, the results were similar in all the subgroup of patients considered in the review (Table 3) but were less marked for patients pre-treated with clopidogrel (OR 0.80, 95% CI 0.67 to 0.95; Analysis 7.4) .

Secondary endpoints

Data on urgent revascularization and the combined endpoint of death, myocardial infarction or urgent revascularization at 30 days were available from 35 trials with 30,433 patients (98% of patients included in the overall review), and from 23 trials with 20,360 patients (66% of patients included in the overall review) at six months.

Urgent revascularization

Urgent revascularization occurred in 2.05% of patients in the treatment group versus 3.47% in controls at 30 days, and in 12.88% and 15.64% respectively at 6 months.Treatment with intravenous GP IIb/IIIa blockers was associated with a reduction in the risk of urgent revascularization at 30 days (OR 0.61, 95% CI 0.53 to 0.70, P<0.00001; I^2 = 17%) and at 6 months (OR 0.86, 95% CI 0.79 to 0.94, P = 0.0004; I^2 = 9%). At 30 days, results were less marked for patients with stable CAD (OR 0.84, 95% CI 0.54 to 1.32) and for those pre-treated with clopidogrel (OR 0.85, 95% CI 0.60 to 1.21), especially in patients without ACS, while at 6 months, the results were similar in all subgroups (Table 4).

Death, MI or urgent revascularization

The combined endpoint of death, MI or urgent revascularization at 30 days and six months was of 6.68% vs. 9.76% and 18.96% vs. 23.53% in the treatment and control groups respectively. IIb/IIIa blockers were also associated with a lower risk of death, MI or urgent revascularization both at 30 days (OR 0.64, 95% CI 0.57 to 0.73) and at six months (OR 0.78, 95% CI 0.71 to 0.87), although the analysis showed a marked heterogeneity of the results both at 30 days (I^2 = 39%) and at six months (I^2 = 44%). Again, the global results were similar to those obtained in all subgroups but were less marked for the subgroup of patients pre-treated with clopidogrel (30-day OR 0.81, 95% CI 0.68 to 0.97; 6-month OR 0.87, 95% CI 0.77 to 0.97), especially in patients without ACS (Table 4).

Safety

Data were available from 35 trials with 30,528 patients (98% of patients included in the overall review). Major bleeding occurred in 3.03% of patients in the treatment group versus 2.24% in controls. Treatment with intravenous GP IIb/IIIa blockers was associated with an increased risk of severe bleeding (OR 1.38, 95% CI 1.20 to 1.59; P < 0.0001; I^2 = 17%; Analysis 1.9; Figure 7). The absolute risk increase per thousand treated patients over 30 days was of 8.0 (95% CI 4.4 to 11.6) and the NNH of 126. The results were homogeneous in all subgroups (Analysis 7.9), and also in studies with or without blinding (Table 5).

2. GP IIb/IIIa blockers as initial medical treatment in patients with non-ST segment elevation acute coronary syndromes

Primary endpoints

Data from 10 trials with 31,069 patients (100% of patients included in this meta-analysis) were available on 30-day mortality and myocardial infarction, while data from only 4 trials but with 14,051 patients (45% of patients included in the overall review) were available on 6-month mortality and myocardial infarction.

Mortality occurred in 3.34% of patients in the treatment group versus 3.59% in controls at 30 days, and in 6.30%

and 6.27% respectively at 6 months. Death or MI occurred in 10.59% and 11.93% at 30 days, and 13.32% and 14.59% at 6 months respectively.

Treatment with intravenous GP IIb/IIIa blockers did not decrease the risk of mortality at 30 days (OR 0.91, 95% CI 0.80 to 1.03; P = 0.13; I^2 = 6%; Analysis 8.1), and at six months (OR 1.00, 95% CI 0.87 to 1.15; I^2 = 0%). However, these agents reduced the risk of mortality and/or myocardial infarction both at 30 days (OR 0.92, 95% CI 0.86 to 0.99, P = 0.02; I^2 = 1%; Analysis 8.3), and at six months (OR 0.88, 95% CI 0.81 to 0.96; I^2 = 0%). At 30 days, the ARR per thousand treated patients was of 13.4 (95% CI 6.3 to 20.5) and the NNT of 75, while at six months they were of 12.7 (95% CI 2.9 to 22.5) and 79 respectively.

Safety

Data were available from 10 trials with 30,638 patients (98.6% of patients included in the overall review). Treatment with intravenous GP IIb/IIIa blockers was associated with an increase in the incidence of severe bleeding at 30 days (OR 1.27, 95% CI 1.12 to 1.43, P = 0.0001; Analysis 8.5). Major bleeding occurred in 3.81% and in 3.67% of patients in the treatment and control groups, respectively. The absolute risk increase per thousand treated patients over 30 days was of 1.4 (95% CI -2.9 to 5.6).

Summary of analyses

The main results for the primary outcomes can be found in Table 3, the main results for the secondary outcomes in Table 4 and the main results for safety outcomes in Table 5.

Discussion

GP IIb/IIIa blockers during PCI

This systematic review has identified that GP IIb/IIIa blockers may be safe and effective when administered during PCI with or without stent implantation. This is based on data from 38 trials including over 31,000 patients. Overall, the administration of IIb/IIIa blockers as a bolus immediately before the intervention followed by a 12 to 24-hour infusion is beneficial. Although associated with an increased risk of severe bleeding (8.0 per 1000), this hazard may be considered to be offset by the reduction in the 30-day mortality (4.1 patients per 1000 treated), mortality or non-fatal myocardial infarction (24 patients per 1000), and the need for urgent revascularization (14 patients per 1000 treated). In addition, the results also indicate that the early benefit of GP IIb/IIIa blockers is maintained at six months for all endpoints.

Most of the beneficial effects of these drugs were on the prevention of peri-procedural MI, condition whose definition has varied along the years and between studies partially because troponins have only been included in their diagnosis in studies performed after year 2005. In addition, their diagnosis is especially difficult in patients presenting with an MI. Although we tried to limit the variability of the definition by using a uniform criteria of an elevation >3 times the upper limit of normal of the used biomarker of necrosis when the data was obtainable, the variability of the MI definition could explain the heterogeneity observed in the analysis of this endpoint.

The beneficial effect of these drugs is homogeneous in different subgroups of patients according to their clinical condition (i.e. stable CAD, NSTEACS or STEMI), and the technique used (i.e. balloon angioplasty or PCI with stent), although 30-day and 6-month mortality was only reduced when administered in procedures with stent implantation. The use of drug-eluting stents have been reported to be associated with a higher risk of thrombosis. Since no study on IIb/IIIa blockers has been performed specifically in patients with drug-eluting stents, and since in only four of the 24 reviewed studies (BRAVE-3 2009; CLEAR PLATELETS-2 2009; ISAR-REACT 2 2006; OPTIMIZE-IT 2009) a drug-eluting stent was used in more than 40% of the cases, the results of this meta-analysis only applies to patients in which a bare metal stent was implanted.

The administration of clopidogrel before PCI in addition to aspirin and heparin, and during the first year following PCI has shown to reduce the risk of acute coronary occlusion and of mortality, myocardial infarction or recurrent ischaemia (PCI-CURE 2001), and is currently the standard medical treatment of patients subjected to this procedure (ACC/AHA 2007; ESC 2007). In recent years, the administration of clopidogrel in addition to aspirin and heparin has also been shown to be of benefit as initial medical treatment of patients with NSTEACS (ACC/AHA 2007; CURE 2001; ESC 2007; PCI-CURE 2001). Currently one of the main controversies in clinical cardiology is the effectiveness of GP IIb/IIIa blockers in patients submitted to PCI on chronic clopidogrel treatment or in patients pre-treated with a loading dose from the time of hospital admission or at least two to six hours before PCI.

Eleven trials including 8,058 patients analysed the efficacy of these drugs in this setting. One of these trials was performed in patients with NSTEACS (ISAR-REACT 2 2006), three in patients with STEMI (BRAVE-3 2009, On-TIME 2004, Shen 2008), five in patients with stable CAD (Claeys 2005; ISAR-REACT 2004; ISAR-SWEET 2004; ISAR-SMART-2 2004; TOPSTAR 2002), and two others in a mixed population with most patients with (ADVANCE 2004) and without ACS (ASIAD 2005). The results of this systematic review show that IIb/IIIa blockers are less efficacious in decreasing major and minor events in patients pre-treated with clopidogrel, and suggest that they retain a beneficial effect only in patients with ACS. On the other hand, the risk of severe bleeding was not enhanced.

GP IIb/IIIa blockers as initial medical treatment in patients with non-ST segment elevation acute

coronary syndromes

This systematic review also identified that GP IIb/IIIa antagonists are safe but much less effective when administered as an initial medical treatment to patients with NSTEACS than in patients who underwent PCI. This conclusion is based on data from over 31,000 patients. Overall, the administration of intravenous GP IIb/IIIa blockers as an initial bolus followed by a continuous infusion for 24 to 72 hours resulted in a modest benefit at 30 days (13.4 deaths or myocardial infarctions prevented per 1,000 patients treated) and at six months. This benefit was obtained in spite of a very acceptable excess of severe bleeding (1.4 per 1,000). However, the treatment provided no significant benefit on all-cause mortality at 30 days or six months.

These results contrast with those mentioned above in the overall population submitted to PCI, and also in the subgroup of patients with NSTEACS that underwent PCI. It is worth noting that except for two studies (PRACTICE 2007; PRISM 1998) the beneficial effect obtained was higher in trials with a high use rate of PCI procedures than in trials with a low frequency of these procedures. In addition, in two trials (PRISM Plus 1998; PURSUIT 1998) patients that underwent PCI 24 to 72 hours after admission obtained greater benefit from GP IIb/IIIa antagonists after PCI than before the procedure (Boersma 1999), and in one trial (PARAGON B 2002), a benefit was observed only among patients that underwent PCI during drug infusion. These results strongly suggest the existence of a positive interaction between PCI and the effect of GP IIb/IIIa blockers. Finally, because the overall treatment effect of GP IIb/IIIa inhibitors when administered as initial medical management of patients with NSTEACS is small and these drugs are expensive, the best cost-effectiveness ratio may be obtained when they are administered in high-risk patients scheduled for early PCI. In this sense, a recent trial has shown similar effects of one of these drugs (eptifibatide) when administered since hospital admission (upstream treatment) than during early PCI (downstream treatment) (EARLY-ACS 2009).

It is important to note that in spite of the proven effectiveness of these drugs, they are administered in less than half of the patients submitted to PCI and in only one third of patients with a NSTEACS (CRUSADE 2006; GRACE 2007), and some data even show that these drugs are less often offered to high-risk patients (GRACE 2007). Further applied clinical research would be desirable to enlarge the administration of these drugs to high-risk patients as recommended in current guidelines (ESC 2007; ACC/AHA 2007; NICE 2002).

Characteristics and limitations of the review

Heterogeneity of studies was statistically important only in nine of the 96 analyses performed, all of them related to PCI and seven regarding secondary endpoints. Such heterogeneity is likely to be due to the subjective nature of urgent revascularization. Differences in patient's characteristics as age, gender, history of myocardial infarction, proportion of patients with acute coronary syndromes, although important, did not result in significant statistical heterogeneity. It is unlikely that other factors such as drug dosages or important concomitant treatments may have affected homogeneity, particularly heparin and aspirin.

We did not perform a cost-effectiveness analysis since this was out of the scope of our review. Some of the analysed studies performed a retrospective analysis on cost-effectiveness, most of them with data from a specific country and applying the results of the overall study. It is to note that this kind of analysis is difficult to perform in multicenter trials in which participating countries have major differences in local practices and public health policies and economies.

It should be noted that the studied population may not be representative of all patients undergoing PCI or with NSTEACS in clinical practice. In the group of patients treated during PCI the mean age of patients was lower than what it is usually observed in clinical practice, as well as the proportion of other co morbidities (CRUSADE 2006; GRACE 2007). However, the subgroup analysis performed on these patients showed similar results than those obtained in the global analysis and those obtained in patients with or without stable CAD. In the group of patients with NSTEACS treated medically, the inclusion was limited to patients with ST-segment changes during the admission ECG or with positive biological markers of myocardial necrosis. These features are present in three fourths of patients and are know to select high-risk patients. In fact, in most university centres patients with these characteristics are submitted to coronary angiography within 48 hours as currently recommended (ACC/AHA 2007; ESC 2007). In addition, some studies have shown a significant interaction between GP IIb/IIIa blockers and the presence of positive troponin levels at admission (Boersma 2002). On the other hand, all of these randomised controlled trials excluded patients with significant renal impairment, cerebrovascular disease and also any patient with a moderate to high risk for bleeding complications. For these reasons, the generalisability of the findings of this review is limited to a moderate to high-risk population with a low risk of bleeding complications.

Authors' conclusions

Implications for practice

Intravenous IIb/IIIa blockers administered during PCI reduce the risk of death and of death or MI at 30 days and at six months, at a price of an increase in the risk of severe bleeding. The efficacy effects are homogeneous for all subgroup of patients although they are less marked in patients pre-treated with clopidogrel, where they seem to be effective only in patients with an Acute Coronary Syndrome.

When administered as initial medical treatment in patients with NSTEACS, these agents do not reduce all cause mortality, but slightly reduce the risk of death or myocardial infarction at 30 days and at six months and increase

the risk of severe bleeding.

Implications for research

Since the analysis of patients that underwent PCI after pre-treatment with clopidogrel showed less benefit than in the main analysis, and since new oral antiplatelet agents as prasugrel and ticagrelor have been shown to be more efficacious than clopidogrel (PLATO 2009; TRITON TIMI-38 2007) but with a higher risk of bleeding (TRITON TIMI-38 2007), further trials are warranted in patients pre-treated with these drugs. Also, further research is needed to analyse if the favourable effects observed in patients in which a bare metal stent is implanted will also be observed in patients with drug-eluting stents.

Also and considering the cost of these drugs, prospective cost-effectiveness analyses in patients managed with current recommendations (ACC/AHA 2007; ESC 2007) will be desirable. In addition, patient-centred outcomes as quality of life have not been studied and are particularly warranted.

This review did not consider trials performed in patients with STEMI during facilitated thrombolysis or facilitated or rescue PCI (De Luca 2008). The number of trials performed in these settings is growing and their results variable, making further research desirable on this high-risk population.

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Contributions of authors

Xavier Bosch originated and was primarily responsible for planning, designing and carrying out the primary version of the review and the 2007 and 2010 updates. He was the principal author and prepared the results and the clinical discussion of the findings.
Juan Sanchis participated in reviewing the studies of the 2010 update and in the discussion of the results.
Jaume Marrugat participated in the design, the methodology and the discussion of the primary version of the review and in the discussion of the 2007 update.
In each version, two of the three authors participated in the study selection, review of pre-selected studies, data extraction and in the preparation of the manuscript.

Declarations of interest

Xavier Bosch participated as investigator in the PRISM Plus 1998, GUSTO-IV 2001, and EARLY-ACS 2009 studies. He has no other potential conflicts of interest to declare.

Jaume Marrugat has no potential conflict of interest to declare.

Juan Sanchis participated as investigator in the EARLY-ACS 2009 study.

Differences between protocol and review

Published notes

Characteristics of studies

Characteristics of included studies

3T/2R 2009

Methods	Method of treatment allocation: An independent study nurse at each site performed assignments of study treatments via a procedure using sealed envelopes, in preselected blocks of six. Double-blinded?: Yes. Stratification: Yes, according to the presence of stable or unstable coronary artery disease and poor responsiveness to aspirin, clopidogrel, or both. Placebo: yes. Sample size calculation: No. Intention-to-treat analysis: Yes. Funding: partially supported by a research grant from Merck, USA, and Iroko, USA.
Participants	Location: Ten centres in Italy, Belgium, France and Spain. Timeframe: From February 2006 to June 2008. Follow-up: 30 days. Eligibility criteria: 263 patients >18 ys scheduled for coronary angiography, PCI, or both who presented with stable or troponin-negative NSTEACS, and showed poor ex-vivo response to aspirin or clopidogrel. Exclusion criteria: any evidence of myocardial damage as witnessed by a rise of cardiac specific injury markers and ongoing MI, defined as the presence of ST-segment elevation at ECG or new or presumably new left bundle-branch block. Mean age: 68 ys, 74% male, 26% diabetes, 43% prior MI. ACS: 32% (Unstable Angina: 32%, Non-STEMI: 0%, STEMI: 0%). PCI: 100% (balloon angioplasty: 7%, stent: 93%, drug-eluting stents: ?%), pre-treatment with Clopidogrel: 100%.
Interventions	Tirofiban (bolus of 25 mg/kg plus a 14 to 24-h infusion of 0.15 mg/kg/min) vs. Placebo (bolus and infusion). 93 patients were low-responders to aspirin, 147 to clopidogrel and 23 to both. Screening for clopidogrel response was undertaken in patients at steady state for aspirin provided at least one of the following two requirements was fulfilled: the patient received a 600- or 300-mg loading dose ≥2 or 6 hours before, respectively, or the patient received a 75-mg maintenance clopidogrel dose for ≥7 consecutive days.
Outcomes	Primary: Rate of periprocedural MI. Secondary: 30-day occurrence of minor myocardial injury, the composite of death, MI, or urgent target vessel revascularization, and the incidence of stent thrombosis.
Notes	Screening for clopidogrel response was undertaken in patients at steady state for aspirin provided at least one of the following two requirements was fulfilled: the patient received a 600- or 300-mg loading dose ?2 or 6 hours before, respectively, or the patient received a 75-mg maintenance clopidogrel dose for ≥7 consecutive days.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Referring to a random number generator
Allocation concealment?	Yes	An independent study nurse at each site performed assignments of study treatments via a procedure using sealed envelopes, in preselected blocks of six.
Blinding? Primary	Yes	Double-blinded study with a placebo group. Mortality and myocardial infarction adjudicated by an independent clinical events committee.
Blinding? Secondary	Yes	Major bleeding assessed by TIMI criteria and adjudicated by an independent clinical events committee
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The published reports include all the prespecified outcomes
Free of other bias?	Unclear	The study was partially supported by a research grant from Merck, USA, and Iroko, USA

ACE 2003

Methods	Method of treatment allocation: By means of a computer generated sequence, and assignments were made using a centralized telephone system. Double-blinded?: no (Study not blinded, without a placebo group) Stratification: no. Placebo: no. Sample size calculation: yes Intention-to-treat analysis: yes Funding: SORIN Biomedica and the ARCARD ONLUS Foundation Follow-up: 30 days and six months
Participants	Location: 4 centres in Italy, Argentina and Germany. Timeframe: From January 2001 to August 2002. Eligibility criteria: 400 patients with ST-segment elevation acute myocardial infarction of less than 6 hs or between six and 24 hs if there was evidence of continuing ischaemia, including patients with cardiogenic shock. Exclusion criteria: previous administration of fibrinolytic or abciximab therapy, a history of bleeding diathesis or allergy to the study drug, major surgery within 15 days, active bleeding, participation in another study, and inability to obtain informed consent. Angiographic criteria: IRA reference diameter <2.5 mm, a previously stented IRA; 3) <70% stenosis of the IRA associated with Thrombolysis In Myocardial Infarction (TIMI) trial flow grade 3 (9); and 4) an inability to identify the IRA. Mean age: 66 ys, Male: 78%, Diabetes: 18%, Prior myocardial infarction: 11% Acute coronary syndrome: 100% (Unstable angina: 0%, Non-STEMI: 0%, STEMI: 100%). PCI: Atherectomy: ?%, Balloon angioplasty: 0%, Stent: 99%. Pre-treatment with clopidogrel: 0%.
Interventions	Unblinded abciximab versus placebo. Patients randomised to abciximab received the drug immediately before the procedure as a bolus of 0.25 mg/kg body weight, followed by a 12-h infusion at a rate of 0.125 µg/kg/min.
Outcomes	Primary: A composite of death from any cause, reinfarction, target vessel revascularization, and stroke within one month of the index procedure. Secondary: ST-segment reduction, postprocedural corrected TIMI frame count, infarct size at one month, death from any cause at six months, reinfarction at six months, six-month composite of death and reinfarction, TVR at six months, and angiographic restenosis of the IRA at six months.
Notes	All patients treated with 325 mg of aspirin and heparin. Immediately after the procedure patients received 500 mg of ticlopidine or 300 mg of clopidogrel. Aspirin and clopidogrel 75 mg or ticlopidine 500 mg were maintained for one month.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	By means of a computer generated sequence
Allocation concealment?	Yes	Using a centralized telephone system.
Blinding? Primary	No	Study not blinded and without a placebo group. Events were not adjudicated by an independent clinical events committee
Blinding? Secondary	No	Study not blinded and without a placebo group. Events were not adjudicated by an independent clinical events committee
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The published report include all pre-specified outcomes
Free of other bias?	Unclear	The study was supported by SORIN Biomedica and the ARCARD ONLUS Foundation

ADMIRAL 2001

Methods	Method of treatment allocation: not stated (All the patients were randomly assigned, in the order in which they were enrolled, to receive either abciximab or placebo) Double-blinded?: yes Stratification: none stated. Placebo. Yes. Sample size calculation: yes Intention-to-treat analysis: yes Funding: Supported by Eli Lilly, Saint-Cloud, France, and Indianapolis, and by Saint-Côme-Chirurgie, Marseilles, France. Follow-up: 30 days and six months
Participants	Location: 26 centres in France Timeframe: From July 12,1997, to December 22, 1998. Eligibility criteria: 300 patients with ST-segment elevation acute myocardial infarction of less than 12 hs with coronary anatomy suitable for stent implantation. Exclusion criteria: Exclusion criteria were bleeding diathesis, administration of thrombolytic agents for the current episode, neoplasm, recent stroke, uncontrolled hypertension, recent surgery, oral anticoagulant therapy, a limited life expectancy, childbearing potential, and known contraindications to therapy with aspirin, ticlopidine, or heparin. Mean age: 61 ys, Male: 82%, Prior myocardial infarction: 11%. Acute coronary syndrome: 100 % (Unstable angina: 0%, NSTEMI: 0%, STEMI: 100%). PCI: Atherectomy: ?%, Balloon angioplasty: 13%, Stent: 87%. Pre-treatment with clopidogrel: 0%.
Interventions	Abciximab as a bolus of 0.25 mg per kilogram of body weight, followed by a 12-hour infusion of 0.125 µg per kilogram per minute (maximum, 10 µg per minute) versus placebo.
Outcomes	Primary: A composite of death, myocardial infarction or urgent revascularization at 30 days. Secondary: A composite of death, myocardial infarction or any revascularization at 30 days and at six months; death or myocardial infarction, death, myocardial infarction or urgent revascularization at six months; TIMI flow grade; ejection fraction.
Notes	All patients treated with aspirin, heparin and ticlopidine. The data were retained by Eli Lilly, where the analyses were performed. Independent statistical advice was provided by E. Vicant (Paris VII University). One of the authors, Dr. Pinton, was an employee of and stockholder in Eli Lilly. Dr. Montalescot has served as a consultant to Eli Lilly.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	"All the patients were randomly assigned, in the order in which they were enrolled, to receive either abciximab or placebo"
Allocation concealment?	Unclear	Not stated
Blinding? Primary	Yes	Double-blinded study with a placebo group. "The patients, investigators, and sponsors of the study were blinded to the treatment assignments during the entire study".
Blinding? Secondary	Yes	Double-blinded study with a placebo group. "The patients, investigators, and sponsors of the study were blinded to the treatment assignments during the entire study".
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The published report include all pre-specified outcomes
Free of other bias?	No	The data were retained by Eli Lilly, where the analyses were performed. Independent statistical advice was provided by E. Vicant (Paris VII University). One of the authors, Dr. Pinton, was an employee of and stockholder in Eli Lilly. The principal investigator has served as a consultant to Eli Lilly.

ADVANCE 2004

Methods	Method of treatment allocation: By the use of computer-based 1:1 randomisation scheme by an independent study nurse. Double-blinded?: yes. Stratification: no Placebo: yes. Sample size calculation: yes Intention-to-treat analysis: yes Funding: supported by a grant from Cassa dei Risparmi di Ferrara, Italy Follow-up: six months
Participants	Location: One hospital in Italy (Arcispedale S. Anna Hospital, University of Ferrara). Timeframe: From March 2002 to August 2003. Eligibility criteria: 202 coronary patients undergoing elective or urgent PCI + stent with clinical or angiographic high-risk features. Inclusion criteria were the presence of >1 stenosis >70% amenable to coronary stenting and the presence of diabetes mellitus, or a planned multivessel intervention, or the presence of non-ST-segment elevation ACS. Exclusion criteria: ST-segment elevation myocardial infarction, administration of any GP IIb/IIIa inhibitors during the previous two weeks, serum creatinine ?2.5 mg/dl, ongoing bleeding or bleeding diathesis, previous stroke in the last six months, major surgery within the previous six weeks, and platelet count <100,000 per mm^3. Mean age: 69 ys, Male: 68%, Diabetes: 49%, Prior myocardial infarction: 48% Acute coronary syndrome: 56 % (Unstable angina: ?, NSTEMI: ?, STEMI: 0%) ST-segment depression: ?, CK-MB elevation: ?, Troponin elevation: ? PCI: Atherectomy: ?, Balloon angioplasty: 2%, Stent: 98%. Pre-treatment with clopidogrel: 0%.
Interventions	High-dose bolus tirofiban (25 µg/kg per 3 min) and infusion (0.15 µg/kg/min for 24-48 h) vs. placebo.
Outcomes	Primary: A composite of death, nonfatal MI, urgent TVR, and thrombotic bailout GP IIb/IIIa inhibitor therapy. Secondary: Each component of the primary endpoint, the effects on troponin I release after the procedure and the effects on pre-specified subgroups: diabetes and ACS
Notes	All patients were pretreated with aspirin and a thienopyridine (clopidogrel 300 mg orally 6 hs before the procedure -63%- or ticlopidine 500 mg 48 hs before -37%-).

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Using a computer random number generation
Allocation concealment?	Unclear	"by an independent study nurse".
Blinding? Primary	Unclear	Double-blinded, placebo-controlled study, but the preparation of the placebo was not stated. Some key study personnel were not blinded, and this condition could bias the assessment of myocardial infarction, since no clinical events committee adjudicated the endpoints
Blinding? Secondary	No	Some key study personnel were not blinded, and this condition could bias the assessment of subjective endpoints
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The published report include all pre-specified outcomes
Free of other bias?	Yes	The study appears to be free of other sources of bias

ASIAD 2005

Methods	Method of treatment allocation: By means of a computer-generated randomisation numbers at each centre. Double-blinded?: Yes. Stratification: No. Placebo: yes. Sample size calculation: Yes. Intention-to-treat analysis: Yes. Funding: Guidant, Corporation.
Participants	Location: Seven centres in China (5 in Hong Kong), India and Singapore). N: 254 patients. Timeframe: From January 2001 to October 2002. Follow-up: six months. Eligibility criteria: Type 2 diabetic patients undergoing PCI with planned use of stents to treat de novo ?50% coronary lesions. Exclusion criteria: Platelet count <100,000/L, concurrent warfarin therapy, INR ?1.5, uncontrolled hypertension, stroke in previous two ys, transient ischemic attack in previous six months, intracranial neoplasm, major surgery within six weeks, gastrointestinal bleeding within three months, PCI within three months, myocardial infarction within five days, and target lesion or target vessel proximal to target lesion containing thrombus. Mean age: 61 ys, 74% male, 100% diabetes, 41% prior MI. ACS: 46% (Non-STEACS: 31%, STEMI: 15%). PCI: 100% (balloon angioplasty: 0%, stent: 100%, drug-eluting stents: 0%).
Interventions	Abciximab (bolus of 0.25 mg/kg up to 60 minutes before the intervention followed by a continuous infusion of 0.125 µg/kg/ min for 12 hours) vs. Placebo (bolus and infusion).
Outcomes	Primary: Incidence of angiographic restenosis at 6-months follow-up. Secondary: Major cardiac events (death, MI or target lesion revascularisation) at 6 months.
Notes	Clopidogrel pre-treatment was administered as a 300 mg loading dose at least 12 hs before the procedure, or a 75 mg daily dose five days before the intervention.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	"By means of a computer-generated randomisation numbers at each centre"
Allocation concealment?	Yes	Not specifically stated but probably yes.
Blinding? Primary	Yes	Double-blinded, placebo-controlled study. "patients and investigators were blinded to treatment allocation".
Blinding? Secondary	Yes	Double-blinded, placebo-controlled study. "patients and investigators were blinded to treatment allocation".
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The published report include all pre-specified outcomes
Free of other bias?	Unclear	The study was supported by Guidant, Corporation.

BRAVE-3 2009

Methods	Method of treatment allocation: according to a computer-generated random sequence enclosed in sealed envelopes in the emergency room or intensive care unit of the five participating PCI centres. The size of the block was preselected by the statistician and was unknown to the investigators and medical staff caring for the patients. Double-blinded?: Yes. Stratification: No. Placebo: yes. Sample size calculation: Yes. Intention-to-treat analysis: Yes. Funding: Grants from Deutsches Herzzentrum, Munich, Germany.
Participants	Location: Five centres in Germany and one in Austria. Timeframe: From June 2003 to January 2008. Follow-up: 30 days. Eligibility criteria: 800 patients with acute STEMI presenting <24 hours after the onset of symptoms, or presumed new left bundle-branch block on surface ECG, who gave informed consent. Exclusion criteria: thrombolytic therapy for the index infarction; those with previous stroke within the last three months, active bleeding or bleeding diatheses, recent trauma or major surgery during the last month, suspected aortic dissection, oral anticoagulation therapy with coumarin derivatives within the last seven days, recent use of glycoprotein IIb/IIIa inhibitors within the last 14 days, severe uncontrolled hypertension, haemoglobin <100 g/L or hematocrit <4%, platelet count <100,000/L or >600,000/L), malignancies, prolonged cardiopulmonary resuscitation, or cardiogenic shock; those >80 or <18 years of age; those with known or suspected pregnancy; and those who were allergic to study drugs. Mean age: 62 ys, 74% male, 18% diabetes, 10% prior MI. ACS: 100% (Non-STEACS: 0%, STEMI: 100%). PCI: 100% (balloon angioplasty: 4%, stent: 96%, drug-eluting stents: 44%), pre-treatment with Clopidogrel: 100%.
Interventions	Abciximab (bolus of 0.25 mg/kg followed by a continuous infusion of 0.125 µg/kg/ min (up to a maximal dose of 10 µg/min) for 12 hours) vs. Placebo (bolus and infusion).
Outcomes	Primary: Infarct size in a SPECT study. Secondary: Total death resulting from any cause, recurrent MI, stroke, urgent IRA revascularization at 30 days, and in-hospital incidence of major and minor bleeding complications.
Notes	All patients received 600 mg clopidogrel orally at the emergency room or intensive care unit of the admitting hospital.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	"according to a computer-generated random sequence"
Allocation concealment?	Yes	"enclosed in sealed envelopes in the emergency room or intensive care unit of the 5 participating PCI centres.
Blinding? Primary	Yes	Double-blinded, placebo-controlled study
Blinding? Secondary	Yes	Double-blinded, placebo-controlled study
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	Yes	The study appears to be free of other sources of bias

CADILLAC 2002

Methods	Method of treatment allocation: Not stated (Patients were randomly assigned in a balanced fashion to one of four interventional strategies of reperfusion with the use of a 2-by-2 factorial design: PTCA alone, PTCA plus abciximab, stenting alone, or stenting plus abciximab) Double-blinded?: no. Open label study. Stratification: none stated. Placebo: no Sample size calculation: yes Intention-to-treat analysis: yes Funding: Supported in part by Guidant, Lilly Research Laboratories, and Mallinkrodt. Follow-up: 30 days and one year
Participants	Location: 76 centres in USA and eight European countries Timeframe: From November 1997 to September 1999 Eligibility criteria: 2082 patients with ST-segment elevation acute myocardial infarction of less than 12 h with a coronary stenosis no longer than 64 mm and with a reference diameter of 2.5 to 4 mm. Patients were randomised using a two by two factorial design to undergo PTCA alone, PTCA plus abciximab, stenting alone or stenting plus abciximab. Exclusion criteria: Cardiogenic shock, history of bleeding diathesis or allergy to the study drug; major surgery within the preceding six weeks; gastrointestinal or genitourinary bleeding within the preceding six months; cerebrovascular event within the preceding two years or any permanent residual neurologic defect; history of leukopenia, thrombocytopenia, or hepatic or renal dysfunction; recent treatment with a thrombolytic agent; a non-cardiac illness associated with a life expectancy of less than one year; and participation in another study Mean age: 60 ys, Male: 73%, Diabetes: 16%, Prior myocardial infarction: 14% Acute coronary syndrome: 100 % (Unstable angina: 0%, NSTEMI: 12%, STEMI: 88%) ST-segment depression: 0%, CK-MB elevation: 100%, Troponin elevation: ?%. PCI: Balloon angioplasty: 50%, Stent: 50%. Pre-treatment with clopidogrel : 0%.
Interventions	Abciximab (bolus of 0.25 mg per kilogram of body weight, followed by a 12-hour infusion at a rate of 0.125 µg per kilogram per minute (maximum, 10 µg/minute)) vs. control.
Outcomes	Primary: A composite of death, reinfarction, repeated intervention or revascularization of the target vessel as a result of ischaemia, or disabling stroke during the first six months after the index procedure
Notes	Al patients received 324 mg of aspirin before the procedure, 500 mg ticlopidine or 300 mg clopidogrel orally, a 5000 U bolus of heparin and a beta-blocker i.v. All but two of the authors have received research support from, or have served as consultants to, companies manufacturing interventional devices or pharmaceutical agents relevant to this study. These companies include, but are not limited to, Guidant and Lilly Research Laboratories, two of the sponsors of the study.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	"Patients were randomly assigned in a balanced fashion to one of four interventional strategies of reperfusion with the use of a 2-by-2 factorial design
Allocation concealment?	No	Open-label study
Blinding? Primary	No	In spite of the existence of a clinical events adjudication committee, the open-label nature of the study could bias the assignment of myocardial infarction.
Blinding? Secondary	No	The open-label nature of the study could certainly bias the assignment of subjective outcomes as revascularisation and major bleeding.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	Unclear	"Supported in part by Guidant, Lilly Research Laboratories, and Mallinkrodt".

CANADIAN 1996

Methods	Method of treatment allocation: by sequential numbers generated centrally and incorporated into double-blind labelling. Double-blinded?: yes. Stratification: no Placebo: yes. Sample size calculation: no Intention-to-treat analysis: yes Funding: F. Hoffmann-La Roche Follow-up: 30 days
Participants	Institutions: 15 Canadian centres. Timeframe: not stated Eligibility criteria: 365 patients with unstable angina or myocardial infarction without ST-segment elevation. Exclusion criteria: Age >75 years (380 patients); unstable angina precipitated by identifiable factors (67 patients) or occurring within 6 months of coronary angioplasty or two months after bypass surgery (198 patients); a previous stroke (22 patients); a high bleeding risk including trauma, surgery, or active bleeding within the previous month (89 patients); shock, congestive heart failure, left bundle-branch block, uncontrolled hypertension, a life-threatening concomitant illness, platelet count <100 000/mm^3, use of oral anticoagulants or of an investigational drug, potential for pregnancy, or the inability to obtain informed consent (270 patients). Mean age: 60 y, Male: 72%, Prior myocardial infarction: 55% ACS: 100% (Unstable angina: 86%, Non-STEMI: 14%, STEMI: 0%), ST-segment depression: 65%, CK-MB elevation: 14%, Troponin elevation: ? PCI: In-hospital: not stated, during drug-infusion: not stated. Treatment with clopidogrel: 0%.
Interventions	Dose-ranging study in which patients were randomly assigned to one of five parallel study arms: one with placebo and four with different bolus plus infusion doses of lamifiban: 150 µg plus 1 µg/min, 300 µg plus 2 µg/min, 600 µg plus 4 µg/min, and 750 µg plus 5 µg/min.
Outcomes	Study designed to obtain a first evaluation of lamifiban in patients with unstable angina and to determine an optimal dose of the drug for a subsequent pivotal trial on a large scale
Notes	Dose-ranging trial: all four lamifiban arms were grouped for the analysis. All patients were treated with aspirin.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	"sequential numbers generated centrally"
Allocation concealment?	Yes	"sequential numbers incorporated into double-blind labelling".
Blinding? Primary	Yes	Double-blinded, placebo controlled trial. "Events were all classified by a Critical Event Committee before the study was unblinded. Relevant data and documents without patient/centre identifiers were reviewed independently by a panel of two for all patients with any complication or event."
Blinding? Secondary	Yes	Double-blinded, placebo controlled trial. "Events were all classified by a Critical Event Committee before the study was unblinded. Relevant data and documents without patient/centre identifiers were reviewed independently by a panel of two for all patients with any complication or event".
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	Yes	Probably yes because the trial sponsor (F. Hoffmann-La Roche) and the investigators remained blinded to randomisation code and study results until all study end points had been agreed on by the Critical Event Committee.

CAPTURE 1997

Methods	Method of treatment allocation: Randomisation was obtained by telephone call to an independent service organised by the Department of Clinical Epidemiology of the University of Amsterdam. Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: yes Intention-to-treat analysis: yes Funding: Not stated. Follow-up: 30 days and six months
Participants	Location: 69 centres in 12 countries (Netherlands, Germany, France, Belgium, Spain, UK, Italy, Israel, Switzerland, Canada, Portugal, Austria). Timeframe: From May 1993 to December 1995. Eligibility criteria: 1,265 patients with refractory unstable angina who underwent percutaneous transluminal coronary angioplasty. Exclusion criteria: Recent myocardial infarction, persisting ischaemia that would require immediate intervention; a greater than 50% occlusion of the left main coronary artery or a culprit lesion located in a bypass graft; bleeding risk factors such as surgery, gastrointestinal or genitourinary bleeding during the 6 weeks before enrolment, or a cerebrovascular accident within the previous 2 years; planned administration of oral anticoagulants or a thrombolytic agent before or during PTCA; underlying medical conditions such as persistent hypertension despite treatment; history of haemorrhagic diathesis; history of autoimmune disease, or a platelet count below 100x109/L. Mean age: 61 ys, Male: 72%, Prior myocardial infarction: 50%. Acute coronary syndrome: 100% (Unstable angina: 100%, NSTEMI: 0%, STEMI: 0%) ST-Segment depression: ?, CK-MB elevation: 0%, Troponin elevation: ?. PCI: Balloon angioplasty: 98%, Stent: 1%. Pre-treatment with clopidogrel: 0%.
Interventions	Abciximab (0·25 mg/kg bolus followed by a continuous infusion of 10 µg/min) vs. matching placebo.
Outcomes	Primary: 30-day incidence of death (from any cause), myocardial infarction, or an urgent intervention for treatment of recurrent ischaemia. Secondary: Each component of the composite end point, and bleeding.
Notes	Intervention began 18 to 24 hs before percutaneous transluminal coronary angioplasty and continued until 1h after it. Permits assessment of the effect of GP IIb/IIIa blockers as initial medical treatment of unstable angina and also during percutaneous transluminal coronary angioplasty. The trial was discontinued on the recommendation of the Safety and Efficacy Monitoring Committee after interim analysis of 1050 patients (planned 1400 patients).

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Using a computer random number generator
Allocation concealment?	Yes	"Randomisation was obtained by telephone call to an independent service organised by the Department of Clinical Epidemiology of the University of Amsterdam.
Blinding? Primary	Yes	Double-blinded, placebo controlled trial.
Blinding? Secondary	Yes	Double-blinded, placebo controlled trial.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	No	The trial was discontinued after the third interim analysis of 1050 patients (1400 planned) by the Safety and Efficacy Monitoring Committee

Chen 2000

Methods	Method of treatment allocation: Not stated. Double-blinded ?: yes. Stratification: no. Placebo: yes. Sample size calculation: no. Intention-to-treat analysis: no. Funding: Not stated. Follow-up: 30 days
Participants	Location: One centre in Taiwan (The Veterans General Hospital, Taipei). Timeframe: From January 1997 to July 1997. Eligibility criteria: 42 coronary patients scheduled to undergo coronary angioplasty. They were eligible if they had early postinfarction angina or unstable angina with >=2 episodes of angina at rest associated with ECG changes during the previous 24 hs; or clinical or angiographic characteristics indicating high risk according to the AHA/ACC criteria. Exclusion criteria: Patients >80 ys old, bleeding diatheses, major surgery within prior 6 weeks, stroke within prior 2 ys, planned stent implantation or atherectomy. Mean age: 70 ys, Male: 95%, Diabetes:35%, Prior myocardial infarction: 46% Acute coronary syndrome: 29% (Unstable angina: 29%, NSTEMI: ?%, STEMI: 0%). PCI: Balloon angioplasty: 100%, Stent: 0%. Pre-treatment with clopidogrel: 0%.
Interventions	Abciximab (bolus of 0.25 mg/kg, followed by an infusion of 10 mg/min for 12 hs) vs. placebo
Outcomes	Primary: 30-day incidence of the composite endpoint of death, nonfatal myocardial infarction, unplanned surgical or repeated percutaneous revascularization, or insertion of an intra-aortic balloon pump for refractory ischemia. Secondary: Each component of the composite end point, and bleeding.
Notes	Small study performed in 42 Chinese patients.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Not stated.
Allocation concealment?	Unclear	Not stated. "Patients were randomly assigned in a double-blind fashion to one of the two treatment groups".
Blinding? Primary	Unclear	"Double-blinded, placebo-controlled study", but no specific methods reported.
Blinding? Secondary	Unclear	"Double-blinded, placebo-controlled study", but no specific methods reported.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	Unclear	To few explanations in the study report

Claeys 2005

Methods	Method of treatment allocation: Not stated. Double-blinded ?: No. Stratification: no. Placebo: No. Sample size calculation: no. Intention-to-treat analysis: no. Funding: Sanofi-Synthelabo, Belgium, and Dade Behring, Belgium. Follow-up: 30 days and six months
Participants	Location: One centre in Belgium: Antwerp University Hospital, Antwerp, Belgium.. Timeframe: From October 2001 to November 2003. Eligibility criteria: 200 patients scheduled for elective PCI with stent implantation and pre-treated with aspirin and a loading dose of clopidogrel (450 mg) were randomised just before coronary intervention to treatment with or without abciximab. Exclusion criteria: Acute coronary syndromes requiring urgent coronary intervention or early treatment with GP IIb/ IIIa receptor antagonists, recent myocardial infarction, intervention of lesions located in bypass grafts or near major side branches, presence of an angiographically visible intracoronary thrombus, patients with creatinine value >2.0 mg/dL, with haemostatic disorders, or with a history of intolerance to thienopyridines or to abciximab. Mean age: 67 ys, Male: 70%, Prior myocardial infarction: 19% Acute coronary syndrome: 33% (Unstable angina: 31%, NSTEMI: 0%, STEMI: 0%). PCI: Balloon angioplasty: 2%, Stent: 98%. Pre-treatment with clopidogrel: 100%.
Interventions	Abciximab (bolus of 0.25 mg/Kg, followed by an infusion of 0.125 µg/Kg/min for 12 hs) vs. Placebo. All patients treated with 160 mg ASA, unfractioned heparin, and Clopidogrel at randomisation. Abciximab was administered just before intervention as an intravenous bolus (0.25 µg/kg) followed by a 12-h infusion (10 µg/min).
Outcomes	Primary: level of platelet aggregation inhibition, and of peri-procedural myonecrosis. Secondary: A composite endpoint of death, MI or urgent target-vessel revascularization within 30 days of randomisation.
Notes	Low-risk patients scheduled for elective PCI with stent placement. All patients pretreated with high-dose clopidogrel (300 mg) in the evening preceding PCI and 150 mg in the morning of the intervention.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated.
Blinding? Primary	No	The open-label nature of the study could influence the diagnosis of myocardial infarction.
Blinding? Secondary	No	Open-label study
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	Unclear	Funding: Sanofi-Synthelabo, Belgium, and Dade Behring, Belgium.

CLEAR PLATELETS-2 2009

Methods	Method of treatment allocation: by a computer-generated assignment. Double-blinded?: No, open-label study. Stratification: Yes, according to clopidogrel therapy before PCI. Placebo: No. Sample size calculation: Yes. Intention-to-treat analysis: No. Funding: a research grant from Integrated Therapeutics Group, Inc., a subsidiary of Schering-Plough Corporation.
Participants	Location: Two centres in USA. Timeframe: From March 2006 to December 2007. Follow-up: 30 days and six months. Eligibility criteria: Two hundred consecutive stable patients undergoing PCI. Exclusion criteria: age <18 ys, history of bleeding diathesis, MI within 48 hs, elevated cardiac markers of necrosis, cerebrovascular event within 3 months, chronic vessel occlusion, visible thrombus, illicit drug or alcohol abuse, prothrombin time >1.5 times control, platelet count <100,000/mm^3, hematocrit <30%, creatinine >2.0 mg/dl, and anticoagulation therapy or GP IIb/IIIa blocker use before the procedure. Mean age: 64 ys, 61% male, 41% diabetes, 36% prior MI. ACS: 0%. PCI: 100% (balloon angioplasty: 3%, stent: 97%, drug-eluting stents: 72%), pre-treatment with Clopidogrel: 100%.
Interventions	Eptifibatide plus bivalirudin (n=98) vs. bivalirudin alone (n=102) stratified by prior clopidogrel treatment, thus providing four treatment groups: 1) 600-mg clopidogrel plus bivalirudin; 2) 75-mg clopidogrel plus bivalirudin; 3) 600-mg clopidogrel plus bivalirudin plus eptifibatide; and 4) 75-mg clopidogrel plus bivalirudin plus eptifibatide. Clopidogrel naive patients (n=128) received treatment with 600-mg clopidogrel in the catheterization laboratory immediately after stenting, whereas patients currently on 75-mg (n=72) did not receive a load. Eptifibatide was administered as a double bolus (180 µg/kg) followed by an infusion (2 µg/kg/min) for 18 hs after the procedure.
Outcomes	Primary: Effects on platelet reactivity measured by turbidometric aggregometry and thrombin-induced platelet-fibrin clot strength measured by thrombelastography in PCI patients. Secondary: To study the relation of platelet aggregation and thrombin-induced platelet-fibrin clot strength to the occurrence of periprocedural infarction.
Notes	All patients received clopidogrel therapy. Clopidogrel naive patients received treatment with 600-mg clopidogrel in the catheterization laboratory immediately after stenting. 72% received a drug-eluting stent.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	by a computer-generated random numbers.
Allocation concealment?	Yes	by a computer-generated assignment. Details previously published
Blinding? Primary	No	open-label study.
Blinding? Secondary	No	open-label study.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	Unclear	Funding: a research grant from Integrated Therapeutics Group, Inc., a subsidiary of Schering-Plough Corporation.

Cuisset 2008

Methods	Method of treatment allocation: Not stated. Double-blinded?: No, open-label study. Stratification: No. Placebo: No. Sample size calculation: Yes. Intention-to-treat analysis: Yes. Funding:The Assistance Publique Hôpitaux de Marseille.
Participants	Location: One centre in France. Timeframe: Not stated. Follow-up: 30 days. Eligibility criteria: 149 patients older than 18 years with stable angina or a positive functional study with a planned PCI with stent implantation of a de novo lesion in a native coronary Artery. Exclusion criteria: Left ventricular ejection fraction <30%, ACSin the previous month, prior MI in the target vessel related territory, positive biomarkers pre-PCI, platelet count <100 g/l, and history of bleeding diathesis. Mean age: 65 ys, 75% male, 38% diabetes, ?% prior MI. ACS: 0%. PCI: 100% (balloon angioplasty: 0%, stent: 100%, drug-eluting stents: ?%), pre-treatment with Clopidogrel: 100%.
Interventions	Abciximab (0.25 mg/kg of body weight bolus, followed by a 0.125 µg/kg/min [maximum, 10 mg/min] infusion for 12 hs) vs. Control.
Outcomes	Primary: Death from any cause, periprocedural myonecrosis, acute or subacute definite or probable stent thrombosis, and recurrent ACS Secondary: Major bleeding.
Notes	Study on patients nonresponders to Clopidogrel therapy. Antiplatelet therapy was administered with loading doses of 600 mg of clopidogrel and 250 mg of aspirin the day before the procedure.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Not stated.
Allocation concealment?	Unclear	Not stated.
Blinding? Primary	No	Open-label study
Blinding? Secondary	No	Open-label study
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	Unclear	Insufficient information

ELISA-2 2006

Methods	Method of treatment allocation: By a computerized randomisation procedure. Double-blinded ?: No. Open-label study. Stratification: No. Placebo: No. Sample size calculation: Yes. Intention-to-treat analysis: No. Funding: Not stated. Follow-up: 30 days
Participants	Location: Three centres in The Netherlands. Timeframe: Not stated. Eligibility criteria: 328 patients with NSTEACS that underwent coronary angiography a median of 23 hs after admission. Exclusion criteria: age >80 ys, persistent ST-segment elevation, previous PCI within the preceding 6 months, cardiogenic shock, or a contraindication for the use of triple antiplatelet therapy or invasive therapy. Mean age: 63 ys, Male: 71%, Diabetes:18%, Prior myocardial infarction: 21% Acute coronary syndrome: 100% (Unstable angina: 22%, NSTEMI: 78%, STEMI: 0%). ST-Segment depression: 61%, CK-MB elevation: ?, Troponin elevation: 78%. PCI: In-hospital: 59%. Balloon angioplasty: 10%, Stent: 49%. Pre-treatment with clopidogrel: 100%.
Interventions	Patients were randomised to pre-treatment with either dual (aspirin, clopidogrel 600 mg) or triple antiplatelet therapy (aspirin, clopidogrel 300 mg, and tirofiban 10 mg/kg bolus, 0.15 mg/kg/min maintenance). Study medication was given in an open-label manner. All patients were scheduled for coronary angiography within 48 hs after admission
Outcomes	Primary: Enzymatic infarct size. Secondary: Initial TIMI flow of the culprit vessel
Notes	Comparison of dual vs. triple antiplatelet pre-treatment in patients with NSTEACS who were planned for early catheterization. All patients were pre-treated with 300 to 600 mg of clopidogrel.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	By a computerized randomisation procedure.
Allocation concealment?	Unclear	Not stated
Blinding? Primary	No	Open-label study.
Blinding? Secondary	No	Open-label study.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	No	44% of the patients in the control group received the intervention before (5%), during (22%) or after (17%) PCI.

EPIC 1994

Methods	Method of treatment allocation: By telephone (Patients were randomly assigned to one of the three treatment groups according to a double-blind study design). Double-blinded ?: yes Stratification: according to their study centre and whether they were having an acute evolving myocardial infarction Placebo: yes Sample size calculation: yes Intention-to-treat analysis: yes Funding: Supported by a grant from Centocor, Inc., Malvern, Pa. Follow-up: 30 days
Participants	Location: 56 institutions in the United States Timeframe: From November 1991 to November 1992 Eligibility criteria: 2,099 patients with unstable angina, angina post myocardial infarction or clinically or angiographically high-risk patients undergoing percutaneous transluminal coronary angioplasty or atherectomy. Exclusion criteria: Age > 80 years old, bleeding diathesis, major surgery within the preceding six weeks, stroke within the preceding two years. Mean age: 61 ys, male: 72%, prior myocardial infarction: 56% Acute coronary syndrome: 100% (Unstable angina: 43%, NSTEMI: ?%, STEMI: 41%). ST-Segment depression: ?, CK-MB elevation: ?, Troponin elevation: ? PCI: Atherectomy: 10%, Balloon angioplasty: 90%, Stent: 0%. Pre-treatment with clopidogrel: 0%.
Interventions	Abciximab bolus (0.25 mg/kg)+ placebo infusion vs. abciximab bolus+infusion (10 µg per minute) vs. placebo bolus and infusion.
Outcomes	Primary endpoint: The 30-day incidence of the composite endpoint of death from any cause, nonfatal myocardial infarction, coronary-artery bypass grafting or repeat percutaneous intervention for acute ischemia, and insertion of a coronary endovascular stent because of procedural failure or placement of an intra-aortic counterpulsation balloon pump to relieve refractory ischemia. Secondary endpoint: Unplanned repeat angioplasty to treat recurrent ischemia, urgent coronary surgery to treat recurrent ischemia or failure of an angioplasty, placement of an intracoronary stent to treat imminent or complete abrupt closure of the vessel undergoing angioplasty, and placement of an intra-aortic balloon pump for recurrent ischemia when a repeat revascularization procedure was contraindicated.
Notes	Excluded bolus-alone arm from analysis. This was the only study using the bolus-alone arm.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	randomisation by telephone
Allocation concealment?	Yes	Not specified but probably correct
Blinding? Primary	Yes	Double-blind, placebo-controlled trial with Clinical Events Committee
Blinding? Secondary	Yes	Double-blind, placebo-controlled trial with Clinical Events Committee
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Unclear	No missing outcome data.
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	Unclear	Supported by a grant from Centocor, Inc., Malvern, Pa.

EPILOG 1997

Methods	Method of treatment allocation: By means of a central telephone hot line. Double-blinded?: yes Stratification: No. Placebo: yes Sample size calculation: yes Intention-to-treat analysis: yes Funding: Centocor, Malvern, Pa.; and Eli Lilly and Company, Indianapolis. Follow-up: 30 days
Participants	Location: 69 clinical sites in the United States and Canada. Timeframe: From February 27, 1995 to December 1995. Eligibility criteria: 2,792 patients with ST-segment elevation acute myocardial infarction, unstable or stable angina undergoing percutaneous transluminal coronary angioplasty. Exclusion criteria: Acute myocardial infarction or unstable angina, planned stent implantation or rotational atherectomy; percutaneous coronary intervention performed within the previous three months; a left-main coronary artery stenosis of more than 50% not protected by collateral vessels; concurrent warfarin therapy or a baseline prothrombin time more than 1.2 times the control value; cerebrovascular accident within the previous two years or a residual neurologic deficit; intracranial neoplasm, aneurysm, or arteriovenous malformation; history of vasculitis, known hemorrhagic diathesis, or active internal bleeding; hypertension, with a systolic blood pressure of more than 180 mm Hg or a diastolic blood pressure of more than 100 mm Hg; and major surgery, gastrointestinal bleeding, or genitourinary bleeding within the previous six weeks. Mean age: 60 ys, male: 72%, prior myocardial infarction: %. Acute coronary syndrome: 69% (Unstable angina: 48%, NSTEMI: ?, STEMI: ?). ST-Segment depression: ?, CK-MB elevation: ?, Troponin elevation: ?. PCI: Atherectomy: 5%, Balloon angioplasty: 95%, Stent: 11%. Pre-treatment with clopidogrel: 0%.
Interventions	Abciximab + low-dose heparin vs. abciximab + standard dose heparin vs. placebo + standard dose heparin. For those receiving abciximab, a bolus of 0.25 mg per kilogram of body weight was administered followed by an infusion of 0.125 *m*g per kilogram per minute (maximum, 10 *m*g per minute) for 12 hours.
Outcomes	Primary endpoint: A composite of death from any cause, myocardial infarction or reinfarction, or severe myocardial ischemia requiring urgent coronary bypass surgery or repeated percutaneous coronary revascularization within 30 days after randomisation. Secondary endpoints: A composite of death, myocardial infarction, or coronary bypass surgery or repeated percutaneous revascularization (urgent or non-urgent) within six months after randomisation.
Notes	The two abciximab groups have been grouped together for the analysis

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Not specified "by a central telephone", but probably correct.
Allocation concealment?	Yes	By means of a central telephone hot line.
Blinding? Primary	Yes	Double-blind, placebo-controlled trial with Clinical Events Committee. "To preserve the blinding of all investigators and personnel involved in patient care, a heparin coordinator at each clinical site performed all measurements of activated clotting time and directed the administration of heparin"
Blinding? Secondary	Yes	Double-blind, placebo-controlled trial with Clinical Events Committee
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Unclear	The published reports include all pre-specified and expected outcomes
Free of other bias?	No	The study was stopped after enrolment of 2792 of the planned 4800 patients after the recommendation of the Data and Safety Monitoring Committee Funding: Centocor, Malvern, Pa.; and Eli Lilly and Company, Indianapolis.

EPISTENT 1998

Methods	Method of treatment allocation: By a telephone hotline Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: yes Intention-to-treat analysis: yes. Funding: Centocor, Malvern PA, USA. Follow-up: 30 days
Participants	Institutions: 63 centres in the USA and Canada. Timeframe: Not stated. Eligibility criteria: 2,399 patients scheduled to elective or urgent coronary angioplasty or stent. Exclusion criteria: Unprotected left-main stenosis, bleeding diathesis, intracranial neoplasm, a history of stroke in the previous 2 years, uncontrolled hypertension (systolic blood pressure >180 mm Hg, diastolic >100 mm Hg), recent surgery, or percutaneous coronary intervention within the previous 3 months, concurrent warfarin therapy or an INR>1.5 at baseline. Mean age: 59 ys, male: 75%, prior myocardial infarction: 35%. Acute coronary syndrome: 52% (Unstable angina: 36%, NSTEMI: ?, STEMI: ?). ST-Segment depression: ?, CK-MB elevation: ?, Troponin elevation: ?. PCI: Balloon angioplasty: 29%, Stent: 71%. Pre-treatment with clopidogrel: 0%.
Interventions	Abciximab+stent vs. abciximab+ balloon coronary angioplasty vs. placebo+stent. Patients were randomly assigned stent plus placebo (n=809), stent plus abciximab (n=794), or balloon angioplasty plus abciximab (n=796). Patients received abciximab 0·25 mg/kg body weight, followed by an infusion of 0·125 µg/kg every min (maximum 10 µg/min) for 12 hs.
Outcomes	Primary endpoint: A combination of death from any cause, myocardial infarction or reinfarction, or severe myocardial ischaemia requiring urgent coronary artery bypass surgery or revascularization within 30 days of intervention. Secondary endpoints: Death or myocardial infarction, and death or large, myocardial infarction.
Notes	All patients treated with aspirin and heparin. The stent group received also ticlopidine 250 mg twice daily starting at the discretion of the investigator before the start of the study agent

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	By computer generation
Allocation concealment?	Yes	randomisation by telephone. "The study drug allocation was concealed from patients and investigators". "The masking of the study drug allocation was maintained through the 1-year follow-up".
Blinding? Primary	Yes	Double-blind, placebo-controlled trial with Clinical Events Committee.
Blinding? Secondary	Yes	Double-blind, placebo-controlled trial with Clinical Events Committee
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	Unclear	Study sponsored by Centocor, Malvern PA, USA.

ERASER 1999

Methods	Method of treatment allocation: Into 1 of 3 groups by sealed envelopes provided by the coordinating centre. Double-blinded ?: yes. Stratification: no. Placebo: yes. Sample size calculation: yes Intention-to-treat analysis: no Funding: not stated. Follow-up: hospitalisation and six months
Participants	Institutions: 17 centres from nine countries (USA, Canada, Israel, Italy, Germany, France, Belgium, UK, Netherlands). Timeframe: From May 1996 to February 1997. Eligibility criteria: 215 angina patients with one lesion suitable for stent implantation (>/=50% reduction in intraluminal diameter) in an artery with an intraluminal diameter from 2.75 to 3 mm. Excluded were patients with acute coronary syndrome < 72 hours. Exclusion criteria: Myocardial infarction within 72 hours before randomisation, evident intracoronary thrombus, previous coronary intervention on a non-target lesion within the past 6 months, planned debulking before stent placement, expected inability to access the target lesion by IVUS, or standard contraindications to the use of abciximab. Mean age: 60 ys, male: 79%, prior myocardial infarction: ?. Acute coronary syndrome: 56% (see exclusions) (Unstable angina: 56%, NSTEMI: 0%, STEMI: 0%). ST-Segment depression: ?, CK-MB elevation: ?, Troponin elevation: ? PCI: Balloon angioplasty: 0%, Stent: 100%. Pre-treatment with clopidogrel: 0%.
Interventions	Three different treatment regimens: placebo bolus+2 consecutive 12-hour placebo infusions; abciximab 0.25 mg/kg bolus+0.125 µg · kg^{-1} · min^{-1} (up to 10 µg/min maximum) continuous infusion for 12 hours followed by 12-hour placebo infusion; or abciximab 0.25 mg/kg bolus+2 consecutive 12-hour 0.125 µg · kg^{-1} · min^{-1} (up to 10 µg/min maximum) infusions.
Outcomes	Primary efficacy criterion: percent in-stent volume obstruction of the target lesion, measured at 6 months by IVUS. Primary safety objectives: major bleeding not associated with bypass surgery, and mortality and intracranial haemorrhage through 6 months. Secondary efficacy objectives: Target lesion mean and minimum lumen diameter, late loss and loss index by QCA at 6 months, and a composite of death, myocardial infarction, and TLR within 6 months.
Notes	The 12-h and 24-h infusion groups were grouped together for the analysis. In-hospital was considered 30-day in this review. All patients treated with aspirin and heparin. Ticlopidine use was left to the investigator's discretion.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Computer random number generator
Allocation concealment?	Yes	by sealed envelopes provided by the coordinating centre.
Blinding? Primary	Yes	Double-blind, placebo-controlled trial.
Blinding? Secondary	Yes	Double-blind, placebo-controlled trial.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	Yes	The study appears to be free of other sources of bias

ESPRIT 2000

Methods	Method of treatment allocation: generated with random permuted blocks within each investigative site, with one to one allocation of treatments. Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: yes Intention-to-treat analysis: yes. Funding: COR Therapeutics, South San Francisco, CA, USA, and Schering-Plough Corporation, Kenilworth, NJ, USA. Follow-up: 30 days
Participants	Institutions: 92 centres in USA and Canada. Timeframe: From June 3, 1999, to February 4, 2000. Eligibility criteria: 2,064 patients with coronary artery disease undergoing stent implantation on a native coronary artery. Exclusion criteria: Acute myocardial infarction; continuing chest pain precipitating urgent referral for PCI; PCI within the previous 90 days; previous stent implantation at the target lesion; anticipated staged PCI, treatment with a glycoprotein IIb/IIIa inhibitor or a thienopyridine, stroke or transient ischaemic attack within 30 days before randomisation; any history of haemorrhagic stroke; history of bleeding diathesis or evidence of abnormal bleeding within the previous 30 days; major surgery within the previous 6 weeks; uncontrolled hypertension; documented thrombocytopenia; or a serum creatinine greater than 350 mmol/L. Mean age: 62 ys, male: 73%, prior myocardial infarction: 32%. Acute coronary syndrome: 18% (Unstable angina: 14%, NSTEMI: ?, STEMI: 5%) ST-segment depression: ?, CK-MB elevation: ?, Troponin elevation: ?. PCI: Balloon angioplasty: 3%, Stent: 96%. Pre-treatment with clopidogrel: 0%.
Interventions	Eptifibatide was delivered as two boluses and an infusion. The first bolus of 180 µg/kg was immediately followed by initiation of a 2·0 mg/kg/min (or 1(g/kg/min in patients with serum creatinine values greater than 177 (mol/L) continuous infusion. A second bolus of 180 (g/kg was given 10 min after the first. The infusion was continued until hospital discharge or up to 18?24 h.
Outcomes	Primary endpoint: The composite of death, myocardial infarction, urgent target vessel revascularization, and thrombotic bailout glycoprotein IIb/IIIa inhibitor therapy within 48 h after randomisation. Secondary endpoint: The composite of death, myocardial infarction, and urgent target vessel revascularization within 30 days after randomisation.
Notes	All patients treated with aspirin, heparin and clopidogrel or ticlopidine. Sample size calculation was based on a predicted reduction in the rate of the key 30 day secondary composite efficacy endpoint, rather than the primary endpoint.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Computer random number generator
Allocation concealment?	Yes	Study drugs were packaged to be indistinguishable, irrespective of content
Blinding? Primary	Yes	Double-blind, placebo-controlled trial.
Blinding? Secondary	Yes	Double-blind, placebo-controlled trial.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	No	The data and safety monitoring board recommended to stop the trial after 2064 patients were enrolled (2400 planned). Funding: COR Therapeutics, South San Francisco, CA, USA, and Schering-Plough Corporation, Kenilworth, NJ, USA.

Fu 2008

Methods	Method of treatment allocation: Not stated. Double-blinded?: Yes. Stratification: No. Placebo: yes. Sample size calculation: No. Intention-to-treat analysis: No. Funding: A grant from the NaturalScience Foundation of Hebei Province(No. C2004000615).
Participants	Location: One centre in China Timeframe: From January 2005 to May 2007. Follow-up: 6 months. Eligibility criteria: 150 patients with acute STEMI (or documented new left bundle-branch block) presenting <12 hours after the onset of symptoms and with coronary anatomy suitable for PCI. Exclusion criteria: bleeding diathesis, administration of thrombolytic agents, neoplasm, recent stroke, uncontrolled hypertension, recent surgery, oral anticoagulant therapy and known contraindications to therapy with aspirin, clopidogrel, tirofiban or heparin. Mean age: 53 ys, 68% male, 19% diabetes,?% prior MI. ACS: 100% (Non-STEACS: 0%, STEMI: 100%). PCI: 100% (balloon angioplasty:?%, stent: ?%, drug-eluting stents: ?%), pre-treatment with Clopidogrel: 100%.
Interventions	Tirofiban (bolus of 10 ?g/kg over 3 minutes followed by continuous infusion of 0.15 ?g/kg/min for 24 hours) vs, Placebo (bolus and infusion). All patients treated with 300 mg of Clopidogrel at enrolment.
Outcomes	Primary: Not clear ("to evaluate the effect and safety of tirofiban in STEMI patients undergoing PCI via transradial approach").. Secondary: Not stated.
Notes	Chinese study. All patients treated with 300 mg of Clopidogrel at enrolment.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Not stated and probably not done since the number of patients in each group were different.
Allocation concealment?	Unclear	Not stated
Blinding? Primary	Unclear	patients were blinded with placebo (infusion of saline). Unclear information about blinding of investigators.
Blinding? Secondary	Unclear	patients were blinded with placebo (infusion of saline). Unclear information about blinding of investigators.
Incomplete outcome data addressed? Primary	Unclear	No missing outcome data seem to be present although the extremely good results obtained in the intervention arm raises serious doubts on the methods used.
Incomplete outcome data addressed? Secondary	Unclear	No missing outcome data seem to be present although the extremely good results obtained in the intervention arm raises serious doubts on the methods used.
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	No	The extremely good results obtained in the intervention arm raises serious doubts on the methods used in this trial

Galassi 1999

Methods	Method of treatment allocation: With a standard list of random numbers. Double-blinded?: no, open label study. Stratification: no. Placebo: no. Sample size calculation: no. Intention-to-treat analysis: no. Funding: not stated. Follow-up: 30 days
Participants	Location: One centre in Italy. Timeframe: From October 1996 to February 1998. Eligibility criteria: 106 patients with CAD, demonstrable ischemia and a target de novo complex lesion stenosis >70% in a native vessel scheduled for elective implantation of a >20 mm stent or multiple stents. Exclusion criteria: Acute myocardial infarction; bleeding diathesis, thrombocytopenia, history of stroke, active internal bleeding, severe uncontrolled hypertension, major surgery or trauma within 6 weeks. Male: 88%, mean age: 62 ys, diabetes: 27%, previous MI: 67%, ACS: 0%. Balloon angioplasty: 0%, stent: 100%, drug-eluting stents: 0%. Pre-treatment with clopidogrel: 0%.
Interventions	Patients were randomly assigned, in an open label fashion, to receive either a combination of abciximab (bolus and a 12 hs infusion) and weight-adjusted low-dose heparin or weight-adjusted heparin alone. All patients received 325 mg of aspirin the fay before the procedure and daily thereafter. Ticlopidine 250 mg twice daily was started the day before the intervention and was given to all patients for the first four weeks.
Outcomes	No Primary outcome was specified. Outcomes: mortality, MI, urgent revascularization, target lesion revascularization, acute or subacute stent thrombosis.
Notes	Patients were 'randomly allocated'. There is not description of the allocation concealment or the primary outcome of the study.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Patients were "randomly allocated. . . with a standard list of random numbers".
Allocation concealment?	No	There is not description of the allocation concealment. Probably not used.
Blinding? Primary	No	open-label study
Blinding? Secondary	No	open-label study
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The published reports include all pre-specified and expected outcomes
Free of other bias?	No	No primary outcome was specified.

GUSTO-IV 2001

Methods	Method of treatment allocation: via a centralised interactive voice-response system. Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: yes. Intention-to-treat analysis: yes. Funding: Centocor Inc, Malvern, Pa. Follow-up: 30 days

Participants	Location: 458 hospitals in 24 countries: Australia, Austria, Belgium, Canada, Czech Republic, Finland, France, Germany, Greece, Ireland, Israel, Italy, Netherlands, New Zealand, Norway, Poland, Portugal, South Africa, Spain, Sweden, Switzerland, UK, USA. Timeframe: from July 17, 1998, to April 21, 2000 Eligibility criteria: 7,800 average-risk patients with unstable angina or non-ST segment elevation myocardial infarction. Last episode of chest pain: <24 hs Indicator of myocardial ischaemia: >0.5 mm ST depression or >0.5 mm transient ST elevation or troponin T or I elevation above ULN. Exclusion criteria: myocardial ischaemia precipitated by a disorder other than atherosclerotic CAD, STEMI, new left-bundle branch block; PCI within previous 14 days; planned PCI or coronary bypass surgery within 30 days after enrolment; active internal bleeding or history of haemorrhagic diathesis; major surgery, serious trauma or gastrointestinal or genitourinary bleeding of clinical significance within the previous six weeks; intracranial neoplasm or aneurysm, history of stroke within 2 years, or prior stroke with a residual neurological deficit; oral anticoagulation within the previous 7 days; platelet count of less than 100 000/mL; confirmed hypertension; history of vasculitis; puncture of non-compressible vessel within 24 h before enrolment; allergy to abciximab; weight more than 120 kg; a coexisting disorder associated with limited life expectancy; and participation in another investigational trial within seven days. Mean age: 65 ys, Male: 62%, Prior myocardial infarction: 31%, diabetes: 22%. Acute coronary syndrome: 100% (Unstable angina: 72%, Non-STEMI: 28%, STEMI: 0%), ST-segment depression: 80%, CK-MB elevation: 28%, Troponin elevation: 59% PCI: In-hospital: 19%, during drug-infusion: 1.6%. CABG: 11%. Treatment with clopidogrel: 0%.
Interventions	Abciximab bolus+48-h infusion vs. abciximab bolus + 24-h infusion vs. placebo Dose: a) 250 ng/kg bolus + 0.125 ng/kg/min infusion (maximum 0.10 ng/min) for 24 hs+ heparin b) 250 ng/kg bolus + 0.125 ng/kg/min infusion (maximum 0.10 ng/min) for 48 hs+ heparin c) placebo + heparin Duration: 24 or 48 hs
Outcomes	Primary: Death or myocardial infarction at 30 days. Secondary: Death or myocardial infarction in patients with positive troponin levels; death, myocardial infarction, revascularization or coronary angiography at 48 hs, 7 days, and 30 days; death or myocardial infarction within 30 days. Required level of CK or CK-MB elevation in MI definition: 3xULN. Safety: Intracranial haemorrhage; bleeding leading to decrease in haemoglobin concentration >50g/L.
Notes	GUSTO-IV Study Both abciximab groups were analysed together in this review. All patients treated with 150-325 mg aspirin. Heparin was part of study regimen; initial dose weight-adjusted (maximum 5000 U bolus + 800 U/hs infusion aiming for aPTT of 50-70s; a subgroup treated with dalteparin (maximum dose 10000 U) Angiography was discouraged during infusion period. PCI was not scheduled (just 1.6% had PCI within 48h).

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	using a computer random number generator
Allocation concealment?	Yes	via a centralised interactive voice-response system.
Blinding? Primary	Yes	Double-blind, placebo-controlled study. A clinical endpoint committee, the members of which were unaware of treatment assignment, adjudicated all possible cases of myocardial infarction and the cause of death.
Blinding? Secondary	Yes	Double-blind, placebo-controlled study
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Free of other bias?	Yes	This study was supported by Centocor Inc, Malvern, Pa. "Full independence of the analyses and control over publication remain with the authors, along with the responsibility for any errors". The study appears to be free of other sources of bias.

IMPACT 1995

Methods	Method of treatment allocation: Not stated. Double-blinded ?: yes. Stratification: no. Placebo: yes. Sample size calculation: no Intention-to-treat analysis: yes. Funding: COR Therapeutics, Inc, South San Francisco, USA. Follow-up: 30 days
Participants	Institutions: 11 centres in USA. Timeframe: Not stated. Eligibility criteria: 150 patients with coronary artery disease scheduled for elective percutaneous coronary revascularization. Exclusion criteria: Known history of bleeding disorder, recent gastrointestinal bleeding, major surgery within six weeks, history of stroke or other central nervous system structural abnormality, severe hypertension, pregnancy, elevation of baseline prothrombin time (>1.2 times control), hematocrit <30%, platelet count <100 000/µL, or creatinine >4.0 mg/dl. Mean age: 62 ys, male: 75%, prior myocardial infarction: 45%. Acute coronary syndrome: 75% (Unstable angina: 58%, Non-STEMI: ?%, STEMI: 17%) ST-segment depression: ?%, CK-MB elevation: ?%, Troponin elevation: ?%. PCI: Atherectomy: 13%, Balloon angioplasty: 100%, Stent: 0%. Pre-treatment with clopidogrel: 0%.
Interventions	Eptifibatide bolus (90 µg/kg) + 12-h infusion (1.0-µg · kg^{-1} · min^{-1} for 4 hours) vs. eptifibatide bolus + 4-h infusion vs. placebo.
Outcomes	Primary: A composite of total death, myocardial infarction and urgent coronary revascularization. Secondary: Safety and bleeding complications.
Notes	A phase II study. The two eptifibatide groups were grouped together for the meta-analysis. All patients treated with aspirin and heparin

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	No information provided, but probably yes.
Allocation concealment?	Unclear	No information provided.
Blinding? Primary	Yes	Double-blind, placebo-controlled phase II clinical trial. "All clinical end points were adjudicated by blinded review"
Blinding? Secondary	Unclear	Uncertain since the proportion of major bleeding was 4 times higher in patients in the placebo group than in the intervention group and inversely correlated with minor bleeding
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The study protocol is not available but the published report include all expected outcomes, including those that were pre-specified
Free of other bias?	Unclear	Funding: COR Therapeutics, Inc, South San Francisco, USA.

IMPACT-II 1997

Methods	Method of treatment allocation: Generated by computer in blocks of nine. Assignment was done at the same time as registration and enrolment by telephone call to the Duke Coordinating Center. Double-blinded?: yes. Stratification: yes, patients were stratified according to the perceived risk of ischaemic complications into high-risk and low-risk categories. Placebo: yes. Sample size calculation: yes. Intention-to-treat analysis: yes. Funding: COR Therapeutics, Inc (South San Francisco, California) and Schering-Plough, Inc (Kenilworth, New Jersey). Follow-up: 30 days
Participants	Institutions: 82 centres in the USA Timeframe: from Nov 30, 1993, to Nov 9, 1994. Eligibility criteria: 4,010 patients with coronary artery disease undergoing percutaneous revascularization. Exclusion criteria: history of bleeding diathesis, severe hypertension, major surgery within the previous 6 weeks, history of stroke or other disorders of the central nervous system, pregnancy, gastrointestinal or genitourinary bleeding within the previous 30 days, or other major illness. Mean age: 61 ys, male: 75%, prior myocardial infarction: 41%. Acute coronary syndrome: 42% (Unstable angina: 38%, Non-STEMI: ? %, STEMI: 4%. ST-segment depression: ?%, CK-MB elevation: ?%, Troponin elevation: ?%. PCI: Atherectomy: 23%, Balloon angioplasty: 92%, Stent: 4%. Pre-treatment with clopidogrel: 0%.
Interventions	Bolus of 135 µg/kg eptifibatide followed by an infusion of 0.5 mg/kg/min for 20-24 hs vs. a 135 mg/kg eptifibatide bolus followed by an infusion of 0.75 mg/kg/min for 20-24 hs vs. placebo bolus plus placebo infusion.
Outcomes	Primary endpoint: the occurrence within 30 days of death, myocardial infarction, urgent or emergency repeat coronary revascularisation, or index placement of an intracoronary stent for abrupt closure. Secondary endpoint: the occurrence of the composite endpoint at the completion of drug infusion (24 hs) and at 6 months, the composite endpoint as determined by the site principal investigators (rather than the Clinical Events Committee), outcomes by risk stratification and actual treatment received, and the frequency of angiographically documented abrupt closure.
Notes	Two arms with different doses of eptifibatide and a placebo arm. The two active treatment arms were grouped in our analysis. All patients received aspirin and heparin

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Generated by computer in blocks of nine
Allocation concealment?	Yes	Study drugs were packaged to be indistinguishable irrespective of content.
Blinding? Primary	Yes	Randomised, double-blind, placebo-controlled clinical trial. All efficacy and safety events were adjudicated by consensus of the Clinical Events Committee, from which treatment assignment was concealed throughout the trial.
Blinding? Secondary	Yes	Double-blind, placebo-controlled trial. Study drugs were packaged to be indistinguishable irrespective of content. All efficacy and safety events were adjudicated by consensus of the Clinical Events Committee, from which treatment assignment was concealed throughout the trial.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The study protocol is not available but the published report include all expected outcomes, including those that were pre-specified
Free of other bias?	Unclear	3500 patients were planned to be enrolled. Analysis of available data at the final interim analysis (after enrolment of 3232 patients and tabulation of endpoint results in 2161 patients) suggested that the placebo event rate was lower than predicted. The Data and Safety Monitoring Board therefore recommended that the sample size be increased to 4000 patients to ensure that the trial would maintain the specified power. Funding: COR Therapeutics, Inc (South San Francisco, California) and Schering-Plough, Inc (Kenilworth, New Jersey).

ISAR-2 2000

Methods	Method of treatment allocation: sealed envelopes. Double-blinded?: no. Patients, but not physicians, were blinded to the assignment of treatment. Stratification: no. Placebo: no. Sample size calculation: yes. Intention-to-treat analysis: yes. Funding: Lilly, Deutschland. Follow-up: 30 days
Participants	Location: one hospital in Germany. Timeframe: not stated. Eligibility criteria: 401 patients with ST-segment elevation acute myocardial infarction undergoing angioplasty with stent implantation within 48 hours after onset of chest pain. Exclusion criteria were inability to give informed consent and contraindications to one of the study drugs. All eligible patients who gave written, informed consent were randomised by means of sealed envelopes. Patients, but not physicians, were blinded to the assignment of treatment. Mean age: 61 ys, male: 76%, prior myocardial infarction: ?%. Acute coronary syndrome: 100% (Unstable angina: 0%, Non-STEMI: 0%, STEMI: 100%) ST-segment depression: 0%, CK-MB elevation: 100%, Troponin elevation: ?%. PCI: Balloon angioplasty: 0%, Stent: 100%. Pre-treatment with clopidogrel: 0%, but 100% with ticlopidine.
Interventions	Patients were randomised to one of two treatment regimens: 1) a bolus of abciximab, 0.25 mg/kg of body weight, followed by continuous infusion, 10 mg/min for 12 hs plus an additional dose of heparin (2,500 U intra-arterially), or heparin, (10,000 U intra-arterially), followed by IV heparin infusion (1,000 U/h), for the first 12 hs after sheath removal.
Outcomes	Primary: Angiographic restenosis at six months Secondary: Clinical restenosis and a composite of death, myocardial infarction and target lesion revascularization at 30 days
Notes	Non-placebo controlled. All patients treated with aspirin, heparin and ticlopidine

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Not stated, but probably correct since all the trials from this group have a very good design
Allocation concealment?	Yes	sealed envelopes.
Blinding? Primary	No	Patients, but not physicians, were blinded to the assignment of treatment.
Blinding? Secondary	No	Patients, but not physicians, were blinded to the assignment of treatment.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The study protocol is not available but the published report include all expected outcomes, including those that were pre-specified.
Free of other bias?	Unclear	Funding: Lilly, Deutschland.

ISAR-REACT 2 2006

Methods	Method of treatment allocation: using sealed envelopes containing the block randomisation sequence for each participating centre. Double-blinded?: yes Stratification: no. Placebo: yes. Sample size calculation: yes. Intention-to-treat analysis: yes. Funding: supported in part by the grant KKF 04-03 from Deutsches Herzzentrum, Munich, Germany. Follow-up: 30 days
Participants	Location: Five centres in Germany, one in Netherlands and one in Brazil. Timeframe: From March 2003 through December 2005. Eligibility criteria: an episode of angina (with an accelerating pattern or prolonged or recurrent episodes at rest or with minimal effort) within the preceding 48 hours, accompanied by an elevated troponin T level or a new finding of ST-segment depression of at least 0.1 mV or transient ST-segment elevation of at least 0.1 mV or new or presumed new bundle-branch block; significant angiographic lesions in a native coronary vessel or venous bypass graft amenable to and requiring a PCI; and written informed consent from the patient. Exclusion criteria: ST-segment elevation acute MI; hemodynamic instability; pericarditis; malignancies with life expectancy less than one year; increased risk of bleeding (stroke within the previous 3 months, active bleeding or bleeding diathesis, recent trauma or major surgery in the last month, suspected aortic dissection); oral anticoagulation with a coumarin derivative within the previous 7 days; receipt of a Gp IIb/IIIa inhibitor within the previous 14 days; uncontrolled hypertension; a hemoglobin level less than 100 g/L or hematocrit less than 34%, or platelet count less than 100,000 cells/?L or greater than 600,000 cells/?L; known allergy to the study medication; and pregnancy (present or suspected). 2022 patients with NSTEACS that underwent PCI in native coronary vessels within 6 hs from diagnosis of ACS and after pretreatment with 600 mg of Clopidogrel >2 hs before PCI. Coronary stenting was the target PCI. Mean age: 66 ys, male: 74%, diabetes 27%, prior myocardial infarction: 24%. ACS: 100% (UA:48%, NSTEMI: 52%, STEMI: 0%). PCI: Balloon angioplasty: 3%, Stent: 97% (BMS: 48%, DES: 49%). Pre-treatment with clopidogrel: 100%.
Interventions	Abciximab (bolus of 0.25 mg/Kg, followed by an infusion of 0.125 µg/Kg/min) vs placebo. All patients treated with ASA, heparin and 600 mg of clopidogrel >2h before the procedure
Outcomes	Primary: All-cause death, MI or urgent target-vessel revascularization within 30 days of randomisation. Safety: Major and minor bleeding, and thrombocytopenia.
Notes	High-risk patients with NSTEACS treated with early (<6 hs) PCI after diagnosis

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	computer generated
Allocation concealment?	Yes	using sealed envelopes containing the block randomisation sequence for each participating centre.
Blinding? Primary	Yes	Double-blinded, placebo-controlled trial. Double-blinding was achieved by using vials of similar appearance in the 2 groups.
Blinding? Secondary	Yes	Double-blinded, placebo-controlled trial. Double-blinding was achieved by using vials of similar appearance in the 2 groups.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Free of other bias?	Yes	The study appears to be free of other sources of bias

ISAR-REACT 2004

Methods	Method of treatment allocation: patients underwent randomisation in a double-blind manner with the use of sealed envelopes containing the block randomisation sequence for each participating centre). Double-blinded?: yes Stratification: no. Placebo: yes. Sample size calculation: yes. Intention-to-treat analysis: yes. Funding: Supported by research grants from Deutsches Herzzentrum, Klinik an der Technischen Universität, Munich, Germany (67-00 and 04-01), and by an unrestricted educational grant from Bristol-Myers Squibb GmbH, Munich, Germany. Follow-up: 30 days and 1 ys.
Participants	Location: four institutions in Germany, one in The Netherlands and one in the USA. Timeframe: From May 2000 and February 2003 Eligibility criteria: 2159 patients with CAD that underwent elective PCI in native coronary vessels and had been pretreated with 600 mg of clopidogrel >2 hs before the intervention. Coronary stenting was the target PCI. Exclusion criteria: Recent myocardial infarction or unstable angina, a target lesion in a venous bypass graft; a chronic occlusion; a target lesion with angiographically visible thrombus; a left ventricular ejection fraction < 30%; haemodynamic instability, insulin-dependent diabetes mellitus, pericarditis, or cancer; stroke in the prior 3 months; active bleeding or bleeding diathesis; trauma or major surgery in the preceding month; suspected aortic dissection; oral anticoagulation therapy or glycoprotein IIb/IIIa inhibitor within the preceding 14 days; severe, uncontrolled hypertension; haemoglobin <10 g/dl or a hematocrit < 34%; a platelet count < 100,000 or > 600,000; a known allergic reaction to the study medication; or child-bearing potential. Mean age: 66 ys, male: 76%, prior myocardial infarction: 33%. Acute coronary syndrome: 0% (Unstable angina: 0%, NSTEMI: 0%, STEMI: 0%) ST-segment depression: ?, CK-MB elevation: 0%, Troponin elevation: 0%. PCI: Balloon angioplasty: 10%, Stent: 90%. Pre-treatment with clopidogrel: 100%.
Interventions	Abciximab (bolus of 0.25 mg/Kg, followed by an infusion of 0.125 µg/Kg/min [maximum, 10 mg per minute] for 12 hours) vs. placebo. All patients treated with ASA and heparin.
Outcomes	Primary: All-cause death, MI or urgent target-vessel revascularization within 30 days of randomisation. Secondary: Major and minor bleeding, and thrombocytopenia.
Notes	Low-risk patients scheduled for elective PCI with stent placement. All patients pretreated with high-dose clopidogrel

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	computer generated
Allocation concealment?	Yes	patients underwent randomisation in a double-blind manner with the use of sealed envelopes containing the block randomisation sequence for each participating centre.
Blinding? Primary	Yes	Double-blinded, placebo-controlled trial. Double-blinding was achieved by using vials of similar appearance in the 2 groups.
Blinding? Secondary	Yes	Double-blinded, placebo-controlled trial. Double-blinding was achieved by using vials of similar appearance in the 2 groups. All events were adjudicated and classified by an event-adjudication committee whose members were unaware of the patients' assigned treatment.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Free of other bias?	Unclear	The study appears to be free of other sources of bias

ISAR-SMART-2 2004

Methods	Method of treatment allocation: sealed envelopes containing the randomisation sequence generated by computer before initiation of the trial were used. Double-blinded?: Yes Stratification: No Placebo: No Sample size calculation: Yes Intention-to-treat analysis: Yes Funding: supported in part by an unrestricted research grant from Krauth medical KG, Hamburg, Germany. Follow-up: one year
Participants	Location: three centres in Germany Timeframe: Not stated Eligibility criteria: 502 patients with stable angina pectoris or a positive exercise test that underwent elective PCI in native coronary vessels <2.5 mm in size and after pretreatment with 600 mg of clopidogrel >2 hs before PCI. Exclusion criteria: Acute coronary syndrome, left main coronary artery, in-stent restenosis, and contraindications to the antithrombotic medication used in the study. Mean age: 66 ys, male: 73%, prior myocardial infarction: 37%. Acute coronary syndrome: 0%. ST-segment depression: ?, CK-MB elevation: 0%, Troponin elevation: 0%. PCI: Balloon angioplasty: 50%, Stent: 50%. Pre-treatment with clopidogrel: 100%.
Interventions	Patients were randomly assigned to be treated with either PC-coated stents (n=253) or PTCA (n=249) and with either abciximab (n=251) or placebo (n=251) with the use of a 2x2 factorial design. Patients randomised to abciximab received a bolus of 0.25 mg/kg, followed by an infusion of 0.125 µg/kg/min (maximum, 10 mg per minute) for 12 hours. All patients treated with ASA, heparin and 600 mg of clopidogrel >2h before the procedure.
Outcomes	Primary: Angiographic restenosis at follow-up angiography. Secondary: Combined incidence of all-cause death and MI as well as target vessel revascularization during 1-year follow-up.
Notes	Low-risk patients scheduled for elective PCI with stent placement. All patients pretreated with high-dose clopidogrel >2h before the procedure.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	computer generated
Allocation concealment?	Yes	sealed envelopes containing the randomisation sequence generated by computer before initiation of the trial
Blinding? Primary	Yes	Double-blind, placebo-controlled study
Blinding? Secondary	Yes	Double-blind, placebo-controlled study
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The study protocol is not available but the published reports include all expected outcomes, including those that were pre-specified
Free of other bias?	Yes	The study appears to be free of other sources of bias

ISAR-SWEET 2004

Methods	Method of treatment allocation: with the use of sealed envelopes containing the randomisation sequence for each participating centre. Double-blinded ?: yes Stratification: no Placebo: yes Sample size calculation: yes Intention-to-treat analysis: yes Funding: research grants by Deutsches Herzzentrum, Klinik an der Technischen Universität, Munich, Germany (H04-01). Follow-up: 30 days and 1 ys.
Participants	Location: three German hospitals Timeframe: between January 2001 and October 2003 Eligibility criteria: 701 diabetic patients with CAD scheduled for elective PCI in native coronary vessels and had been pretreated with 600 mg clopidogrel at least 2 hours before intervention. Coronary stenting was the target PCI. Exclusion criteria: myocardial infarction within the prior 14 days; ACS; target lesion with thrombus or in a venous bypass graft; chronic coronary occlusion; a left ventricular ejection fraction <30%, haemodynamic instability, pericarditis, malignancy, a stroke in the prior three months, active bleeding or bleeding diathesis, recent trauma or major surgery in the last month, a suspected aortic dissection, oral anticoagulation therapy, severe uncontrolled hypertension, haemoglobin <100 g/L or hematocrit <34%, thrombocytopenia, known allergic reaction to the study medication, had received a glycoprotein IIb/IIIa inhibitor within 14 days, or were pregnant (present or suspected). Mean age: 67 ys, male: 74%, prior myocardial infarction: 34%. Acute coronary syndrome: 0% ST-segment depression: ?, CK-MB elevation: 0%, Troponin elevation: 0%. PCI: Balloon angioplasty: 10%, Stent: 90%. Pre-treatment with clopidogrel: 100%.
Interventions	Abciximab (bolus of 0.25 mg/Kg, followed by an infusion for 12 hs of 0.125 µg/Kg/min) vs placebo. All patients treated with ASA and heparin.
Outcomes	Primary endpoint: the cumulative incidence of death from any cause and MI during the first 12 months after randomisation Secondary endpoints: incidence of binary angiographic restenosis, and of target lesion revascularization due to angiographic restenosis and symptoms or signs of ischaemia. Safety: Major and minor bleeding, and thrombocytopenia.
Notes	Patients with diabetes mellitus (29% treated with insulin) scheduled for elective PCI with stent. Patients of both study groups received clopidogrel 600 mg at least 2hours before the percutaneous coronary intervention

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	computer generated
Allocation concealment?	Yes	with the use of sealed envelopes containing the randomisation sequence for each participating centre.
Blinding? Primary	Yes	Double blinding was achieved with the use of vials that appeared similar in the 2 groups. All events were adjudicated and classified by an event adjudication committee blinded to the assigned treatment. All analyses were performed in a blinded manner regarding the randomly assigned treatment. Unblinding of the study groups was done after completion of the statistical analyses. No patient required unblinding because of clinical needs, and no crossovers occurred.
Blinding? Secondary	Yes	Double blinding was achieved with the use of vials that appeared similar in the two groups. All events were adjudicated and classified by an event adjudication committee blinded to the assigned treatment. All analyses were performed in a blinded manner regarding the randomly assigned treatment. Unblinding of the study groups was done after completion of the statistical analyses. No patient required unblinding because of clinical needs, and no crossovers occurred.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The study protocol is not available but the published reports include all expected outcomes, including those that were pre-specified
Free of other bias?	Yes	The study appears to be free of other sources of bias

JEPPORT 2009

Methods	Method of treatment allocation: not stated. Double-blinded?: Yes. Stratification: No. Placebo: yes. Sample size calculation: Yes. Intention-to-treat analysis: Yes. Funding: Not stated.
Participants	Location: 88 centres in Japan. Timeframe: From May 1997 to April 2000. Follow-up: 30 days and 6 months. Eligibility criteria: 973 patients with ACS. Exclusion criteria: Age >75 ys; >100 kg of body weight; scheduled for primary stent placement, directional coronary atherectomy or rotablator; history of thrombocytopenia; bleeding symptoms or bleeding diathesis; undergone surgery in the previous six weeks; cerebrovascular disorder in the previous two ys; ?50% stenosis in the left main trunk of the coronary artery; 3-vessel disease; uncontrolled hypertension or pulmonary hypertension; cardiogenic shock requiring cardiopulmonary resuscitation. Mean age: 61 ys, 81% male, 31% diabetes, ?% prior MI. ACS: 100% (Non-STEACS: 23%, STEMI: 77%). PCI: 100% (balloon angioplasty: 75%, stent: 25%, drug-eluting stents: 0%), pre-treatment with Clopidogrel: 0%.
Interventions	Low-dose abciximab (0.20 mg/kg bolus + 0.125 µg/kg/min infusion for 12 hs) vs. high-dose abciximab (0.25 mg/kg bolus + 0.125 µg/kg/min infusion for 12 hs) vs. placebo (bolus and infusion). Thrombolytic drugs, antiplatelet drugs other than aspirin, anticoagulant drugs other than heparin, PGE1 and its derivatives, dextran, and low-molecular-weight dextran, were prohibited during the 6 months from the start of the investigation.
Outcomes	Primary: 30-day occurrence of death, MI and/or urgent revascularization for recurrence of ischemia. Secondary: six month incidence of major coronary events.
Notes	Aspirin administered before the procedure. Clopidogrel and ticlopidine were not allowed before and during the six month follow-up. After the first 223 patients were enrolled in the study, “overseas authorities” stipulated that the approved intravenous drip infusion dose of abciximab be adjusted according to body weight. The study was resumed one year later with the new standard dose.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	not stated but probably yes because the baseline data were well balanced in the 3 groups
Allocation concealment?	Yes	not stated but probably yes because the baseline data were well balanced in the 3 groups
Blinding? Primary	Yes	Double-blind, placebo-controlled trial
Blinding? Secondary	Yes	Double-blind, placebo-controlled trial
Incomplete outcome data addressed? Primary	Yes	3.6% of the patients excluded because of exclusion criteria or because they did not underwent PCI. However, excluded patients were well balanced in the placebo and intervention groups.
Incomplete outcome data addressed? Secondary	Yes	3.6% of the patients excluded because of exclusion criteria or because they did not underwent PCI. However, excluded patients were well balanced in the placebo and intervention groups.
Free of selective reporting?	Yes	The study protocol is not available but the published reports include all expected outcomes, including those that were pre-specified
Free of other bias?	No	The study was stopped for one year and resumed with the dose of abciximab adjusted according to body weight. In total, the study took eight years to be completed.

Juergens 2002

Methods	Method of treatment allocation: The patient received the next consecutive ascending number allocated to the investigator. Double-blinded ?: Stratification: No. Placebo: yes Sample size calculation: yes Intention-to-treat analysis: yes Funding: Merck & Co, Inc, Follow-up: 30 days
Participants	Location: 59 centres in 24 countries (Argentina, Australia, Austria, Brazil, China, Colombia, Costa Rica, Ecuador, Greece, Lebanon, Malaysia, Mexico, New Zealand, Poland, Portugal, Singapore, Slovenia, South Africa, Spain, Switzerland, Taiwan, Turkey, United Kingdom, and Venezuela). Timeframe: From May 1998 to June 1999. Eligibility criteria: 894 patients scheduled to undergo PTCA with intracoronary stent placement. Exclusion criteria: Thrombolytic therapy within 24 hours of AMI, allergy to or unable to tolerate aspirin or heparin, prior treatment with abciximab within 14 days, ticlopidine, clopidogrel or low-molecular-weight heparin within 12 to 24 hours, PTCA within 14 days or planned repeat PTCA as a staged procedure; unprotected left main stenosis; bleeding disorder within 3 months; persistent hypertension; history of stroke or other intracranial pathology within 1 year; recent major surgery, trauma, or cardiopulmonary resuscitation; active peptic ulcer disease, pericarditis, significant retinopathy, suspected aortic dissection, uncontrolled cardiac arrhythmia, other haemodynamically significant cardiac disease, or other clinically important medical illness that would make survival for the duration of the study unlikely; serum creatinine level >2.5 mg/dL, haemoglobin < 11 g/dL, international normalized ratio >1.5, or a platelet count <150,000/mm3; or unable to give informed consent. Mean age: 59 ys, male: 83%, prior myocardial infarction: 46%. Acute coronary syndrome: 46% (Unstable angina: 46%, NSTEMI: ?, STEMI: 0%. ST-segment depression: ?, CK-MB elevation: 0%, Troponin elevation: 0%. PCI: Balloon angioplasty: 2%, Stent: 98%. Pre-treatment with clopidogrel: 0%.
Interventions	Patients were randomised in a 3:2 ratio to receive tirofiban as an intravenous bolus (10 µg/kg over 3 minutes) and maintenance infusion (0.10 kg/kg per minute for 36 hours) or a bolus and infusion of placebo.
Outcomes	Primary endpoint: proportion of patients with bleeding. Secondary endpoints: death, MI, urgent coronary artery bypass grafting for recurrent ischemia, and urgent repeat percutaneous intervention for recurrent ischemia in the target vessel.
Notes	This was primarily a tolerability study. Three employees of Merck & Co, Inc, assisted in the preparation of the manuscript.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	The patient received the next consecutive ascending number allocated to the investigator.
Allocation concealment?	Yes	Patients and investigators were blinded to treatment assignment through the use of identical-appearing active treatment and placebo.
Blinding? Primary	Yes	Patients and investigators were blinded to treatment assignment through the use of identical-appearing active treatment and placebo. Cardiac events were reviewed and adjudicated by an external Event Classification Committee.
Blinding? Secondary	Unclear	There was no central adjudication of bleeding incidents in spite that bleeding was the primary endpoint. In addition, the number of major bleedings was three times lower in the intervention group than in the placebo group and was inversely correlated with minor bleedings.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The study protocol is not available but the published report include all expected outcomes, including those that were pre-specified
Free of other bias?	No	Four employees of Merck & Co assisted the authors in the preparation of the manuscript. Funding: Merck & Co, Inc.

Kereiakes 1996

Methods	Method of treatment allocation: Three dose regimens of tirofiban were studied in 3 sequential panels. Patients within each panel were randomised to receive either tirofiban or placebo in a 3:1 randomisation design. Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: yes. Intention-to-treat analysis: yes. Funding: not stated. Follow-up: hospitalisation
Participants	Institutions: nine centres in USA. Timeframe: not stated. Eligibility criteria: Men and women >18 and <75 years of age who were scheduled to undergo coronary angioplasty for treatment of 1) rest angina pectoris, 2) recurrent angina, or 3) complex coronary lesion morphology associated with a moderate to high risk of procedural failure. 93 patients were enrolled. Exclusion criteria: women of childbearing potential, thrombolytic therapy within 24 hs of angioplasty, severed diffuse multivessel coronary atherosclerosis, uncontrolled cardiac arrhythmia, increased bleeding risk, history of stroke or other intracranial pathology, severe congestive heart failure or haemodynamic instability and allergy or intolerance to aspirin or heparin. Mean age: 59 ys, male: 82%, prior myocardial infarction: 47%. Acute coronary syndrome: 52% (Unstable angina: 39%, Non-STEMI: 0%, STEMI: 13%. ST-segment depression: ?%, CK-MB elevation: ?%, Troponin elevation: ?%. PCI: Atherectomy: 0%, Balloon angioplasty: 100%, Stent: 0%. Pre-treatment with clopidogrel: 0%.
Interventions	Patients received one of three graduated regimens of tirofiban intravenously with a bolus dose of 5, 10 and 10 µg/Kg and continuous infusion doses of 0.05,0.10 and 0.15 µg/Kg per min, respectively.
Outcomes	Primary composite: death, myocardial infarction and need for urgent revascularization
Notes	Dose-ranging study All tirofiban groups were grouped together for the analysis

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Not stated but probably correct
Allocation concealment?	Yes	Not stated but probably correct
Blinding? Primary	Yes	double-blind, placebo-controlled dose-ranging study
Blinding? Secondary	Yes	double-blind, placebo-controlled dose-ranging study
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The study protocol is not available but the published report include all expected outcomes, including those that were pre-specified
Free of other bias?	Unclear	The study appears to be free of other sources of bias.

On-TIME 2 2008

Methods	Method of treatment allocation: By blinded sealed kits with study drug. All staff and study personnel were blinded to treatment. Kits were distributed among the ambulance services or referring centres in blocks of four. Double-blinded?: Yes. Stratification: No. Placebo: yes. Sample size calculation: Yes. Intention-to-treat analysis: Yes. Funding: Merck (USA).
Participants	Location: 24 centres in The Netherlands, Germany, and Belgium. Timeframe: From June 29,2006 to November 13, 2007. Follow-up: 30 days. Eligibility criteria: 984 patients aged 21-85 ys with acute STEMI presenting <24 hours after the onset of symptoms whi were candidates to undergo primary PCI. Exclusion criteria: known severe renal dysfunction (glomerular filtration rate <30 mL/min or serum creatinine >2·5 mg/dL), therapy resistant cardiogenic shock (systolic blood pressure ?80 mm Hg for >30 min), persistent severe hypertension, contraindication to anticoagulation or increased risk of bleeding, left bundle branch block, pregnant women or women who were breastfeeding, and patients with a life expectancy of less than one year. Mean age: 62 ys, 76% male, 12% diabetes, 9% prior MI. ACS: 100% (Non-STEACS: 0%, STEMI: 100%). PCI: 100% (balloon angioplasty: 10%, stent: 90%, drug-eluting stents: 24%), pre-treatment with Clopidogrel: 100%.
Interventions	Prehospital treatment with tirofiban (25 µg/kg bolus and 0.15 µg/kg/min maintenance infusion for 18 hs) or placebo (bolus plus infusion). All patients received at enrolment aspirin and a 600 mg loading dose of clopidogrel.
Outcomes	Primary: Extent of residual ST-segment deviation at 1 h after PCI. Secondary: The composite of death, recurrent myocardial infarction, urgent target vessel revascularisation, or blinded bail-out use of tirofiban at 30 days.
Notes	All patients received 600 mg clopidogrel orally at enrolment.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	computer generated
Allocation concealment?	Yes	By blinded sealed kits with study drug.
Blinding? Primary	Yes	Double-blinded placebo-controlled study. All staff and study personnel were blinded to treatment. Kits were distributed among the ambulance services or referring centres in blocks of four. A blinded, independent clinical endpoint committee adjudicated all clinical endpoints
Blinding? Secondary	Yes	Double-blinded placebo-controlled study. All staff and study personnel were blinded to treatment. Kits were distributed among the ambulance services or referring centres in blocks of four. An independent Data Safety Monitoring Committee was responsible for identification of safety issues
Incomplete outcome data addressed? Primary	Yes	8% of the patients in the intervention group and 8% in the placebo group were excluded. in addition, 3.6% in both groups were lost on follow-up. However this incomplete data was well balanced in the 2 groups and is expected in this kind of study in which patients with a presumed STEMI are randomised in the ambulance.
Incomplete outcome data addressed? Secondary	Yes	8% of the patients in the intervention group and 8% in the placebo group were excluded. in addition, 3.6% in both groups were lost on follow-up. However this incomplete data was well balanced in the 2 groups and is expected in this kind of study in which patients with a presumed STEMI are randomised in the ambulance.
Free of selective reporting?	Yes	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Free of other bias?	Unclear	Funding: Merck (USA). "The study was investigator initiated. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication".

OPTIMIZE-IT 2009

Methods	Method of treatment allocation: Not clear ("by the use of computer-based 1:1 randomisation). Double-blinded?: No, open randomized study. Stratification: No. Placebo: No. Sample size calculation: Yes, but for an alpha error of 0.10. Intention-to-treat analysis: Yes. Funding: Not stated.
Participants	Location: One centre in Italy. Timeframe: Not stated. Follow-up: six months. Eligibility criteria: 46 diabetic patients CAD undergoing elective PCI. Exclusion criteria: Premenopause, severe renal failure (creatinine >2 mg/dl), known haemorrhagic diathesis or thrombocytopenia, life expectancy < 1 year, or raised troponin levels. Mean age: 66 ys, 72% male, 100% diabetes, 17% prior MI. ACS: 0%. PCI: 100% (balloon angioplasty: 0%, stent: 100%, drug-eluting stents: 67%), pre-treatment with Clopidogrel: ?%.
Interventions	Tirofiban (25 µg/kg bolus plus 0.15 µg/kg/min infusion for 8 hs) vs. Placebo (bolus and infusion). Ticlopidine or clopidogrel (loading dose 300 mg) were administered >24 hs before the procedure.
Outcomes	Primary: Incidence of MI and TIMI flow grade after PCI. Secondary: Peak troponin levels and myocardial blush grade.
Notes	Ticlopidine (?%)or 300 mg loading dose of clopidogrel (?%) were administered >24 hs before the procedure.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	"by the use of computer-based 1:1 randomisation"
Allocation concealment?	No	not stated and probably not
Blinding? Primary	No	open-label study
Blinding? Secondary	No	open-label study
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The study protocol is not available but the published report include all expected outcomes.
Free of other bias?	Yes	The study appears to be free of other sources of bias.

PARAGON A 1998

Methods	Method of treatment allocation: not stated Double-blinded?: yes. Stratification: no Placebo: yes. Sample size calculation: not stated Intention-to-treat analysis: yes Funding: Hoffman La-Roche (Basel, Switzerland). Follow-up: 30 days and six months.
Participants	Institutions: 273 hospitals in 20 countries (Australia, Poland, France, Finland, Belgium, Italy, Canada, USA, New Zealand, Netherlands, Argentina, Iceland, Israel, Denmark, Germany, South Africa, Portugal, Sweden, United Kingdom, Brazil). Timeframe: From August 1995 to May 1996 Eligibility criteria: 2,282 patients with unstable angina or non-ST segment elevation myocardial infarction. Exclusion criteria: Patients on oral anticoagulants, intravenous heparin or recent thrombolytic treatment, active, significant bleeding; contraindication to aspirin or heparin; systolic blood pressure 180 mm Hg or diastolic blood pressure 100 mm Hg despite treatment; serum creatinine level >2 mg/dL; platelet count <100 000/mm^3; cerebrovascular accident within the past year; any history of hemorrhagic stroke, tumor, or intracranial aneurysm; angioplasty within the previous week; or gastrointestinal bleeding, major surgery, or trauma within 1 month, and women of childbearing potential. Mean age: 66 ys, male: 65%, prior myocardial infarction: 35% Acute coronary syndrome: 100% (Unstable angina: 100%, Non-STEMI: ?%, STEMI: 0%). ST-segment depression: ?%, CK-MB elevation: ?%, Troponin elevation: ?% PCI: In-hospital: 14%, during drug-infusion: ? Atherectomy: ?%, Balloon angioplasty: 14%, Stent: ?%. Treatment with clopidogrel: 0%.
Interventions	Low dose lamifiban vs. low dose lamifiban + heparin vs. high dose lamifiban vs. high dose lamifiban + heparin vs. placebo + heparin Dose: a) 300 ng bolus + 1 ng/min infusion + random assignment to heparin or heparin-placebo b) 750 ng bolus + 5 ng/min infusion + random assignment to heparin or heparin-placebo c) placebo + heparin Duration: 72-120 hs; median:72 hs
Outcomes	Primary: death or myocardial infarction at 30 days. Secondary: death, myocardial infarction, disabling stroke, major bleeding and intermediate bleeding; death and myocardial infarction at 6 months and death at 1 year. Required level of CK or CK-MB elevation in MI definition: 2xULN Safety: Intracranial haemorrhage; or bleeding leading to haemodynamic compromise requiring intervention.

Notes	Angiography was discouraged during the first 24 hs. PCI at the discretion of treating physician All lamifiban + heparin groups grouped together in the analysis. For safety reasons, patients were discontinued from study after enrolment if the creatinine was found to be 2 mg/dL, the platelet count decreased by one third and was <100 000/mm^3, or important bleeding occurred.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	computer generated
Allocation concealment?	Yes	By a central telephone
Blinding? Primary	Yes	Double-blinded, placebo-controlled study. Matching heparin-placebo vials were supplied by the same manufacturer. "Systematic blinding of heparin administration and careful control of anticoagulation was achieved by use of a bedside aPTT device that produced encrypted results". A Clinical Events Committee, which consisted of practicing cardiologists, was blinded to treatment assignment and adjudicated all clinical primary and main secondary end point events according to published predefined criteria.
Blinding? Secondary	Yes	Double-blinded, placebo-controlled study. Matching heparin-placebo vials were supplied by the same manufacturer. "Systematic blinding of heparin administration and careful control of anticoagulation was achieved by use of a bedside aPTT device that produced encrypted results". A Clinical Events Committee, which consisted of practicing cardiologists, was blinded to treatment assignment and adjudicated all clinical primary and main secondary end point events according to published predefined criteria.
Incomplete outcome data addressed? Primary	Unclear	Study drug was given to 98.4% of the treatment group and 99.1% of the control group. Drug was terminated early in 13% of the control group and in 19% of the lamifiban-treated patients, most commonly for bleeding or planned surgical revascularization.
Incomplete outcome data addressed? Secondary	Unclear	Study drug was given to 98.4% of the treatment group and 99.1% of the control group. Drug was terminated early in 13% of the control group and in 19% of the lamifiban-treated patients, most commonly for bleeding or planned surgical revascularization.
Free of selective reporting?	Yes	follow-up was completed on 96.8% and 93.3% of patients at 6 months and 1 year, respectively, and were well balanced in the placebo and lamifiban groups.
Free of other bias?	Unclear	Funding: Hoffman La-Roche (Basel, Switzerland).

PARAGON B 2002

Methods	Method of treatment allocation: not stated. Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: yes. Intention-to-treat analysis: yes. Funding: Hoffman La-Roche (Basel, Switzerland). Follow-up: 30 days and 6 months.
Participants	Institutions: 389 centres in 29 countries. Timeframe: From February 1998 to June 1999. Eligibility criteria: 5,225 patients with NSTEACS. Exclusion criteria: Active bleeding (particularly gastrointestinal bleeding within 1 month or history of active ulcer), impaired haemostasis (oral anticoagulation with international normalized ratio >1.5, bleeding disorder such as von Willebrand disease, or thrombocytopenia [<100 000 platelets/µL]), increased bleeding risk (stroke within 12 months, any prior intracranial haemorrhage, tumor or aneurysm, trauma or major surgery within one month, blood pressure >180/100 mm Hg despite treatment), contraindication to aspirin or heparin, planned fibrinolysis or GP IIb/IIIa inhibition, GP IIb/IIIa inhibition within one week, left bundle-branch block or pacemaker use, estimated creatinine clearance <30 ml/min, serious co-morbid disease likely to limit survival, and current enrolment in trials of other investigational drugs or devices. Mean age: 64 ys, male: 66%, prior myocardial infarction: 30%. Acute coronary syndrome: 100% (Unstable angina: 43%, Non-STEMI: 57%, STEMI: 0%). ST-segment depression: 44%, CK-MB elevation: 57%, Troponin elevation: ?%. PCI: In-hospital: 28%, during drug-infusion: 12% Atherectomy: 4%, Balloon angioplasty: 28%, Stent: 21%. Treatment with clopidogrel: 0%.
Interventions	Lamifiban (72 hs infusion) vs. placebo Dose: a) 500 ng bolus + 1-2 ng/min infusion depending on creatinine clearance+ heparin b) placebo + heparin Duration: 72-120 hs
Outcomes	Primary: A composite of death, myocardial infarction or severe recurrent ischaemia at 30 days. Secondary: death or myocardial infarction. Required level of CK or CK-MB elevation in MI definition: 2xULN in spontaneous MI; 3xULN in relation to PCI; 5xULN in relation to CABG. Safety: Intracranial haemorrhage; or bleeding leading to haemodynamic compromise requiring intervention.
Notes	The dose of lamifiban used was the one that had the best results in the previous PARAGON A study. Performance of angiography and PCI at the discretion of treating physician.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	A central telephone
Blinding? Primary	Yes	Randomised, double-blind, placebo-controlled trial. All suspected MIs and severe, recurrent ischemic episodes were independently adjudicated by a clinical events committee (CEC).
Blinding? Secondary	Unclear	Randomised, double-blind, placebo-controlled trial. Revascularization and bleeding outcomes were not adjudicated by a clinical events committee.
Incomplete outcome data addressed? Primary	Yes	Follow-up data were 99.8% complete for the primary end point (99.9% for placebo, 99.7% for lamifiban).
Incomplete outcome data addressed? Secondary	Yes	Follow-up data were 99.8% complete for the primary end point (99.9% for placebo, 99.7% for lamifiban).
Free of selective reporting?	Yes	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
Free of other bias?	Unclear	Following the Data and Safety Monitoring Board recommendation when 1639 patients were accrued, it was decided to augment the original sample by 1200 patients. This study was supported by F. Hoffman-La Roche Ltd, Basel, Switzerland.

PRACTICE 2007

Methods	Method of treatment allocation: not stated ("using a prospective randomisation schedule").. Double-blinded?: yes . Stratification: yes. Placebo: yes. Sample size calculation: yes. Intention-to-treat analysis:. Funding: Schering Plough. Follow-up: 30 days and 6 months.
Participants	Institutions: 46 hospitals (34 in France, 5 in Israel, 4 in Spain, 2 in Denmark, and 1 in Germany). Timeframe: September 2001 to July 2004. Eligibility criteria: 393 patients with ischemic chest pain at rest within last 24 hs associated with ECG changes and elevated Tn I or T. Exclusion criteria: Persistent ST-segment elevation, recent MI, prothrombin time >1.2 times control, INR >2, active bleeding within the previous 30 days, uncontrolled hypertension, major surgery or severe trauma within past six weeks, history of stroke, thrombocytopenia, creatinine clearance <30 ml/min, concomitant use of other GP Iib/IIIa blocker, concomitant severe disease associated with shortened life expectancy or pregnancy. Mean age: 63 ys, 73% males, 22% diabetics, 19% with prior MI. Acute coronary syndrome: 100% (Unstable angina: 0%, Non-ST elevation myocardial infarction: 100%, STEMI: 0%) ST-segment depression: 0%, Troponin elevation: 100%. Coronary angiography: 94%, PCI: 61% (balloon angioplasty: ?%, stent: 45%, drug-eluting stent: ?%).
Interventions	Eptifibatide 180mg/kg bolus + 2µg/kg/min infusion for 72 hs vs. placebo. All patients received aspirin + clopidogrel (loading dose: 300 mg) from randomisation. An invasive strategy was planned within 6 to 48 hs after randomisation.
Outcomes	Primary: A composite of death, MI or urgent revascularization at 30 days. Secondary: Incidence of death, non fatal MI, and recurrent ischemia requiring urgent revascularisation at hospital discharge and at six months.
Notes	First study to evaluate the efficacy of upstream administration of a IIb/IIIa antagonist in patients with NSTEACS pretreated with aspirin and clopidogrel from the time of hospital admission. Study stopped by the promoter because of low enrolment when 49% of planned patients were included.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	not stated ("using a prospective randomisation schedule") but probably yes.
Allocation concealment?	Unclear	not stated
Blinding? Primary	Yes	Double-blind randomised study.
Blinding? Secondary	Yes	Double-blind randomised study.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	No	Because of slow enrolment, the study was stopped by the promoter when 51% of the planned patients were enrolled.
Free of other bias?	Unclear	Funding: Schering Plough.

PRIDE 2001

Methods	Method of treatment allocation: not stated. Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: no. Intention-to-treat analysis: no. Funding: COR Therapeutics, Inc., South San Francisco, California; and Schering-Plough Corp., Kenilworth, New Jersey. Follow-up: 30 d.
Participants	Institutions: 14 centres in USA. Timeframe: From September 1996 to June 1997. Eligibility criteria: 127 coronary patients scheduled to undergo elective PCI. Exclusion criteria: History of a bleeding diathesis, severe hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >100 mm Hg on therapy), major surgery within 6 weeks, history of stroke or other central nervous system disease, pregnancy, gastrointestinal or genitourinary bleeding within 30 days, and any other major co-morbid illness Mean age: 59 ys, male: ?, prior myocardial infarction: 51%. Acute coronary syndrome: 0%. ST-segment depression: 0%. PCI: Atherectomy: 0%, Balloon angioplasty: 55%, Stent: 45%. Pre-treatment with clopidogrel: 0%.
Interventions	Pts randomised to 4 treatment regiments: 1) placebo bolus and infusion; 2) bolus of 135 µg/Kg eptifibatide with a 0.75 µg/Kg/min infusion; 3) bolus of 180 µg/Kg eptifibatide with a 2 µg/Kg/min infusion; 4) bolus of 250 µg/Kg eptifibatide with a 3 µg/Kg/min infusion.
Outcomes	Primary: To explore the pharmacodynamics of high doses of eptifibatide. Secondary: Safety and the composite incidence at 30 days of death, myocardial infarction, or urgent revascularization.
Notes	Dose-ranging study. 45% of patients underwent stent implantation

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	not stated, but probably yes
Allocation concealment?	Unclear	not stated
Blinding? Primary	Unclear	A randomised, double-blind, placebo-controlled small dose-ranging study. The primary endpoints (eptifibatide pharmacokinetics and its effect on the pharmacodynamics of platelet function) were blinded. However no clinical events committee adjudicated the events.
Blinding? Secondary	Unclear	A randomised, double-blind, placebo-controlled small dose-ranging study. The primary endpoints (eptifibatide pharmacokinetics and its effect on the pharmacodynamics of platelet function) were blinded. However no clinical events committee adjudicated the events.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The study protocol is not available but the published report include all expected outcomes.
Free of other bias?	Unclear	supported by COR Therapeutics, Inc., South San Francisco, California; and Schering-Plough Corp., Kenilworth, New Jersey.

PRISM 1998

Methods	Method of treatment allocation: not stated. Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: yes. Intention-to-treat analysis: yes. Funding: Merck CO. Follow-up: 30 days
Participants	Institutions: 128 sites in 25 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Colombia, Costa Rica, Finland, France, Germany, Greece, Israel, Italy, Mexico, Netherlands, New Zealand, Norway, Portugal, South Africa, Spain, Sweden, Switzerland, United Kingdom, United States). Timeframe: from March 1994 to October 1996. Eligibility criteria: 3,232 patients with unstable angina or non-ST segment elevation myocardial infarction Exclusion criteria: Prior thrombolytic therapy within the previous 48 hs, allergy to or intolerance of heparin; serum creatinine > 2.5 mg/dL; active bleeding disorder; history of gastrointestinal bleeding; hematuria; a positive fecal occult- blood test; known coagulopathy; a platelet disorder or a history of thrombocytopenia; persistent systolic blood pressure >180 mm Hg, diastolic blood pressure >110 mm Hg, or both; a history of hemorrhagic cerebrovascular disease or an active intracranial pathologic process; a history of cerebrovascular disease or transient ischemic attack within the previous year; a major surgical procedure within the previous month; active peptic ulceration within the previous three months; or an invasive procedure within 14 days before enrolment that would substantially increase the risk of haemorrhage. Mean age: 62 ys, Male: 68%, prior myocardial infarction: 47%. Acute coronary syndrome: 100% (Unstable angina: 75%, Non-STEMI: 25%, STEMI: 0%) ST-segment depression: 32%, CK-MB elevation: 24%, Troponin elevation: ?% PCI: In-hospital: 21%, during drug-infusion: 2%. Atherectomy: 0%, Balloon angioplasty: 13%, Stent: 8%. Treatment with clopidogrel: 0%.
Interventions	Tirofiban (0.6 ng/Kg bolus for 30 minutes + 0.15 ng/Kg/min infusion for a mean of 47.5 hs + placebo heparin) vs. placebo + heparin bolus and infusion.
Outcomes	Primary: A composite of death, myocardial infarction or refractory ischaemia at 48h. Secondary: A composite of death, myocardial infarction and refractory ischaemia at 7 days. Required level of CK or CK-MB elevation in MI definition: 2xULN Safety: Intracranial haemorrhage; bleeding leading to decrease in haemoglobin concentration >50g/L; or cardiac tamponade.
Notes	Angiography was discouraged during the infusion period. PCI was not scheduled

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Using a computer random number generator.
Allocation concealment?	Yes	Central allocation.
Blinding? Primary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Blinding? Secondary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Free of other bias?	Unclear	At the time of the second interim analysis, after 1350 patients had completed the study, the combined rate of clinical events comprised by the primary end point was lower than expected. Because of this, the steering committee and the data and safety monitoring committee recommended an increase in the sample size from the initial 2000 planned to 3200. Funding: Merck CO.

PRISM Plus 1998

Methods	Method of treatment allocation: locally by means of sealed envelopes. Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: yes. Intention-to-treat analysis: yes. Funding: Merck CO. Follow-up: 30 days
Participants	Institutions: 72 hospitals in 14 countries (Argentina, Australia, Austria, Canada, Chile, Colombia, Denmark, Finland, France, South Africa, Spain, Switzerland, United States, Timeframe: From November 1994 to September 1996. Eligibility criteria: 1,915 High risk patients with unstable angina or non-ST elevation MI. Exclusion criteria: ST-segment elevation lasting more than 20 minutes, coronary angioplasty within the previous 6 months or bypass surgery within the previous month, angina caused by identifiable factors, prior thrombolytic therapy in the previous 48 hs, serum creatinine > 2.5 mg, an active bleeding disorder or a high risk of bleeding, a history of gastrointestinal bleeding, hematuria, known coagulopathy, a platelet disorder or a history of thrombocytopenia, stroke within the previous year, a history of hemorrhagic cerebrovascular disease or an active intracranial pathologic process. Mean age: 63 ys, Male: 67%, Prior myocardial infarction: 43%. Acute coronary syndrome: 100% (Unstable angina: 55%, Non-STEMI: 45%, STEMI: 0%) ST-segment depression: 58%, CK-MB elevation: 45%, Troponin elevation: ?%. PCI: In-hospital: 31%, during drug-infusion: 25%. Atherectomy: ?%, Balloon angioplasty: ?%, Stent: ?%. Treatment with clopidogrel: 0%.
Interventions	High-dose tirofiban (0.6 ng/kg bolus + 0.15 ng/kg/min infusion) + placebo heparin vs. regular dose tirofiban (0.4 ng/Kg bolus + 0.1 ng/Kg/min infusion) + heparin vs. placebo + heparin. Duration of infusion: 48-96 hs.
Outcomes	Primary: A composite of death, myocardial infarction and refractory ischaemia at 7 days. Secondary: The same composite endpoint at 48 hs and 30 days; the components of the primary endpoint as separate measures, and a composite of death or myocardial infarction. Required level of CK or CK-MB elevation in MI definition: 2xULN in spontaneous MI; 3xULN in relation to PCI. Safety: Intracranial haemorrhage; bleeding leading to decrease in haemoglobin concentration >40g/L or transfusion of >=2 U blood; or requiring corrective surgery.
Notes	Angiography was recommended after the first 48 hs of randomisation and during the infusion period (48-96 hs). PCI performed if indicated by angiography. The study in the tirofiban-only group was stopped prematurely on the recommendation of the data and safety monitoring board at the time of the first interim efficacy analysis. This effect disappeared at 6-month follow-up. Both tirofiban groups were grouped together for the analysis.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Using a computer random number generator.
Allocation concealment?	Yes	locally by means of sealed envelopes.
Blinding? Primary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Blinding? Secondary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
Free of other bias?	No	The study in the tirofiban-only group was stopped prematurely on the recommendation of the data and safety monitoring board at the time of the first interim efficacy analysis because of an apparent mortality excess. At that time the sample size of the other two arms was increased to 735 patients per group. Funding: Merck CO.

PURSUIT 1998

Methods	Method of treatment allocation: in a double-blind manner, by coordinating centres in the United States or the Netherlands. Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: yes. Intention-to-treat analysis: yes. Funding: COR Therapeutics and Schering-Plough Research Institute. Follow-up: 30 days
Participants	Location: 726 participating hospitals in 28 countries (United States, Argentina, Uruguay, Austria, Belgium, Canada, Chile, Colombia, Czech Republic, El Salvador, Finland, France, Germany, Greece, Guatemala, Hungary, Italy, Mexico, Norway, Poland, Portugal, Spain, Switzerland, the Netherlands, United Kingdom, Venezuela) Timeframe: From November 1995 to January 1997. Eligibility criteria: 10,948 patients with unstable angina or non-ST segment elevation myocardial infarction Exclusion criteria: Persistent ST-segment elevation of more than 1 mm, active bleeding or a history of bleeding diathesis, gastrointestinal or genitourinary bleeding within 30 days before enrolment, systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg, a history of major surgery within the previous six weeks, a history of non-hemorrhagic stroke within the previous 30 days or any history of hemorrhagic stroke, renal failure, pregnancy, the planned administration of a platelet glycoprotein IIb/IIIa receptor inhibitor or thrombolytic agent, or the receipt of thrombolytic therapy within the previous 24 hours. Mean age: 64 ys, Male: 65%, Prior myocardial infarction: 32%. Acute coronary syndrome: 100% (Unstable angina: 54%, Non-STEMI: 46%, STEMI: 0%) ST-segment depression: 50%, CK-MB elevation: 46%, Troponin elevation: ?%. PCI: In-hospital: 24%, during drug-infusion: 11% Atherectomy: ?%, Balloon angioplasty: 12%, Stent: 12%. Treatment with clopidogrel: 0%.
Interventions	Regular dose eptifibatide (180 µg/kg bolus + 1.3 µg/kg/min infusion) + heparin vs. high-dose eptifibatide (180 ng/kg bolus + 2.0 ng/kg/min infusion) + heparin, vs. placebo + heparin. Duration of infusion: 72-96 hs.
Outcomes	Primary: A composite of death or non-fatal myocardial infarction at 30 days. Secondary: Mortality at 30 days; myocardial infarction at 30 days; death or myocardial infarction at 96 hs and 7 d; bleeding complications. Required level of CK or CK-MB elevation in MI definition: 1xULN in spontaneous MI; 3xULN in relation to PCI; 5xULN in relation to CABG. Safety: Intracranial haemorrhage; or bleeding leading to haemodynamic compromise requiring intervention.
Notes	Angiography and PCI at the discretion of treating physician. After 3218 patients had been randomly assigned to treatment groups, the independent data safety and monitoring committee recommended dropping the lower dose.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Using a computer random number generator
Allocation concealment?	Yes	Centrally by coordinating centres.
Blinding? Primary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Blinding? Secondary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The study protocol is available and all of the studies pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Free of other bias?	Unclear	After 3218 patients had been randomly assigned to treatment groups, the committee recommended dropping the lower dose of the intervention arm. Funding: COR Therapeutics and Schering-Plough Research Institute.

RAPPORT 1998

Methods	Method of treatment allocation: Not stated. Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: yes. Intention-to-treat analysis: yes. Funding: This study was supported by Centocor, Malvern, Pa, and Eli Lilly and Company, Indianapolis, Ind. Follow-up: 30 days and 6 months
Participants	Location: 36 centres in the USA. Timeframe: From November 16, 1995, to February 2, 1997. Eligibility criteria: 483 patients with myocardial infarction (<12 hours) candidates for primary percutaneous transluminal coronary angioplasty. Exclusion criteria: Severe thrombocytopenia, baseline prothrombin time >1.2 times control, ongoing internal bleeding or recent major surgery, previous stroke, severe uncontrolled hypertension, PTCA of the infarct artery within three months, cardiogenic shock or prolonged resuscitation, vasculitis, prior administration of abciximab or fibrinolytic therapy, or inability to give written informed consent. Mean age: 61 ys, male: 72%, prior myocardial infarction: 21%. Acute coronary syndrome: 100% (Unstable angina: 0%, Non-STEMI: 0%, STEMI: 100%. ST-Segment depression: 0%, CK-MB elevation: 100%, Troponin elevation: ?. PCI: Atherectomy: 0%, Balloon angioplasty: 85%, Stent: 7% (unplanned). Pre-treatment with clopidogrel: 0%.
Interventions	Abciximab (0.25 mg/kg bolus followed by a 12-hour infusion of 0.125 mg/kg/min infusion (maximum, 10 mg/min) vs. placebo (bolus and infusion).
Outcomes	Primary: A composite of total death, myocardial infarction and any repeat target vessel revascularization within six months. Secondary: Major bleeding
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Not stated but probably yes because this was a multicenter double-blind placebo controlled trial and the same investigators have performed other well designed and performed trials.
Allocation concealment?	Yes	Not stated but probably yes because this was a multicenter double-blind placebo controlled trial and the same investigators have performed other well designed and performed trials.
Blinding? Primary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Blinding? Secondary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
Free of other bias?	Unclear	Funding: This study was supported by Centocor, Malvern, Pa, and Eli Lilly and Company, Indianapolis, Ind.

RESTORE 1997

Methods	Method of treatment allocation: Not stated. Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: yes. Intention-to-treat analysis: yes. Funding: Merck & Co., Inc., Whitehouse Station, New Jersey. Follow-up: 30 days
Participants	Location: 104 centres in USA and Europe. Timeframe: From January 9 to December 1, 1995. Eligibility criteria: 2,141 patients who were undergoing coronary interventions (balloon angioplasty or DCA) within 72 hours of presentation with an acute coronary syndrome. Exclusion criteria: Thrombolytic therapy within 24 hours, contraindication to anticoagulation, history of a platelet disorder or thrombocytopenia, history of stroke or other intracranial pathology likely to predispose to bleeding, patients scheduled for elective stent placement or angioplasty using a rotablator or transluminal extraction catheter. Mean age: 59 ys, male: 72%, prior myocardial infarction: 35%. Acute coronary syndrome: 100% (Unstable angina: 67%, Non-STEMI: ?, STEMI: 32%. ST-Segment depression: ?, CK-MB elevation: ?, Troponin elevation: ?. PCI: Atherectomy: 8%, Balloon angioplasty: 92%, Stent: 0%. Pre-treatment with clopidogrel: 0%.
Interventions	Tirofiban (10 mg/kg bolus + 0.15 mg/kg/min infusion for 36 hs) vs. placebo.
Outcomes	Primary endpoint: 30-day incidence of a composite endpoint of death from any cause, MI, CABG surgery owing to angioplasty failure or recurrent ischemia, repeat target-vessel angioplasty for recurrent ischemia or insertion of a stent owing to actual or threatened abrupt closure of the target artery. Secondary endpoints: The incidence of all individual endpoints.
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Not stated but probably yes because this was a multicenter double-blind placebo controlled trial and the same investigators have performed other well designed and performed trials.
Allocation concealment?	Yes	Not stated but probably yes because this was a multicenter double-blind placebo controlled trial and the same investigators have performed other well designed and performed trials.
Blinding? Primary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Blinding? Secondary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The study protocol is not available but the published reports include all expected outcomes, including those that were pre-specified.
Free of other bias?	Yes	Funding: Merck & Co., Inc., Whitehouse Station, New Jersey.

Schulman 1996

Methods	Method of treatment allocation: Not stated. Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: no. Intention-to-treat analysis: no. Funding: COR Therapeutics, Inc, San Francisco, California. Follow-up: 30 days.
Participants	Location: 15 centres in USA. Timeframe: not stated. Eligibility criteria: 227 patients with unstable angina and ST-T changes on admission ECG, or known coronary artery disease. Exclusion criteria: Suspected myocardial infarction in evolution, prior coronary artery bypass graft surgery within six months, coronary angioplasty within 72 hours, thrombolytic therapy within 7 days, major surgery within six weeks, a history of cerebral vascular disease, major gastrointestinal or genitourinary bleeding within 30 days, significant thrombocytopenia (<100 000/mm^3), coagulopathy (receiving coumarin or bleeding time >20 minutes), and if they presented with severe hypertension or had renal insufficiency with a creatinine level >4 mg/dL. Mean age: 62 ys, male: 63%, prior myocardial infarction: 55%. ACS: 100% (Unstable angina: 100%, Non-STEMI: 0%, STEMI: 0%). ST-segment depression: 33%, CK-MB or Tn elevation: 0%. PCI: not stated (Atherectomy: ?%, Balloon angioplasty: ?%, Stent: ?%).
Interventions	Low-dose eptifibatide (45-µg/kg bolus over three minutes followed by a continuous 0.5-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion for 24-72 hs) vs. high-dose eptifibatide (90-µg/kg bolus plus infusion of 1 µg/kg/min) vs. Placebo bolus and infusion.
Outcomes	Primary: Number and duration of ischaemic episodes on continuous monitoring over the first 24 hours as well as for the entire duration of drug infusion. Secondary: number and duration of symptomatic ischaemic episodes, ECG episodes of ischaemia after study drug withdrawal, and clinical events of death, myocardial infarction and refractory ischaemia.
Notes	The placebo group received aspirin and heparin while the eptifibatide group received only heparin. Both active treatment groups have been grouped in our analysis

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Not stated but probably yes because this was a multicenter double-blind placebo controlled trial and the same investigators have performed other well designed and performed trials.
Allocation concealment?	Yes	Not stated but probably yes because this was a multicenter double-blind placebo controlled trial and the same investigators have performed other well designed and performed trials.
Blinding? Primary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Blinding? Secondary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The study protocol is not available but the published reports include all expected outcomes, including those that were pre-specified
Free of other bias?	Unclear	Funding: COR Therapeutics, Inc, San Francisco, California.

Shen 2008

Methods	Method of treatment allocation: By a 24-h computer-generated random-allocation system. Double-blinded?: No. Stratification: No. Placebo: yes. Sample size calculation: No. Intention-to-treat analysis: Yes. Funding: a grant from the Shanghai Science and Technology Committee (no. 05DZ19503).
Participants	Location: One centre in China. Timeframe: From January 2005 to June 2006. Follow-up: 30 days and six months. Eligibility criteria: 172 patients with STEMI presenting <12 hs after the onset of symptoms. Exclusion criteria: Cardiogenic shock and known bleeding diathesis. Mean age: 66 ys, 81% male, 27% diabetes,?% prior MI. ACS: 100% (Non-STEACS: 0%, STEMI: 100%). PCI: 100% (balloon angioplasty: 0%, stent: 100%, drug-eluting stents: 100%), pre-treatment with Clopidogrel: 100%.
Interventions	Tirofiban (bolus of 10 mg/kg plus a 36-h infusion of 0.15 mg/kg/min) in the emergency room vs. tirofiban (bolus of 10 mg/kg plus a 36-h infusion of 0.15 mg/kg/min) in the catheterization laboratory vs. Placebo (bolus and infusion). Upon admission, loading doses of aspirin (300 mg) and clopidogrel (450 mg) were given for all patients in the emergency room.
Outcomes	Primary: Occurrence rate of major adverse cardiac events including death, nonfatal MI and target vessel revascularization (either by PCI or coronary artery bypass surgery) at 30-day and 6-month follow-up. Secondary: Hemorrhagic complications and thrombocytopenia.
Notes	All patients treated with drug-eluting stents. Upon admission, loading doses of aspirin (300 mg) and clopidogrel (450 mg) were given for all patients in the emergency room.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	By a 24-h computer-generated random list of numbers.
Allocation concealment?	No	Using an open random allocation schedule.
Blinding? Primary	No	Open-label study
Blinding? Secondary	No	Open-label study
Incomplete outcome data addressed? Primary	Yes	No missing outcome data
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data
Free of selective reporting?	Yes	The study protocol is not available but the published reports include all expected outcomes
Free of other bias?	Unclear	There may be a risk of bias, but there is either: Insufficient information to assess whether an important risk of bias exists

Simoons 1994

Methods	Method of treatment allocation: Not stated. Double-blinded?: yes. Stratification: no. Placebo: yes. Sample size calculation: no. Intention-to-treat analysis: yes. Funding: Centocor, Inc, Malvern, Pa. Follow-up: hospitalisation.
Participants	Location: 7 centres in Europe. Timeframe: From September 1991 to July 1992 Eligibility criteria: 60 refractory unstable angina patients with chest pain at rest despite optimal treatment and a recent (<24 hs) coronary angiography showing a single culprit lesion suitable for PCI were enrolled, provided that a second coronary angiogram, followed by PCI, could be performed 18 to 24 hours after the first (diagnostic) angiogram. Exclusion criteria: features of ongoing ischemia requiring immediate intervention, prior PCI of the same coronary segment within six months, a previous myocardial Q-wave infarction within 7 days, female sex with childbearing potential, recent major trauma including resuscitation, surgery or gastrointestinal or genitourinary bleeding within the past 6 weeks, known hepatic or renal disorder, history of bleeding diathesis or a platelet count of <100 000/mm3, and known autoimmune disorders. Mean age: 60 ys, male: 73%, prior myocardial infarction: 18%. ACS: 100% (NSTEACS: 100%). Transient ST-segment depression or elevation: 67%; CK-MB or Tn elevation: ?%. PCI: Atherectomy: 0%, Balloon angioplasty: 100%, Stent: 0%.
Interventions	Abciximab (0.25 mg/kg bolus + a 10 mg/min infusion) vs. Placebo. The infusion started <4hs after first coronary angiography and was continued until 1 h after PCI, which was scheduled between 18 and 24 hours after the start of the infusion.
Outcomes	Primary: A composite of death, myocardial infarction and recurrent ischaemia requiring urgent intervention (PCI, CABG or intra-aortic balloon pump). Secondary: Occurrence of all recurrent ischemic episodes and angiographic end points.
Notes	All patients treated with i.v. nitroglycerin infusion, aspirin and heparin.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Not stated but probably yes because this was a multicenter double-blind placebo controlled trial and the same investigators have performed other well designed and performed trials.
Allocation concealment?	Yes	Not stated but probably yes because this was a multicenter double-blind placebo controlled trial and the same investigators have performed other well designed and performed trials.
Blinding? Primary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Blinding? Secondary	Yes	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The study protocol is not available but the published reports include all expected outcomes, including those that were pre-specified.
Free of other bias?	Unclear	Funding: Centocor, Inc, Malvern, Pa.

Tamburino 2002

Methods	Method of treatment allocation: By a “standard list of random numbers” with the use of closed envelopes. Double-blinded?: No. Stratification: No. Placebo: No. Sample size calculation: No. Intention-to-treat analysis: Not stated. Funding: Not stated. Follow-up: 30 days and 6 mo.
Participants	Location: Hospital of Catania (Italy). Timeframe: From October 1996 to February 1998. Eligibility criteria: 107 patients with demonstrable reversible ischaemia and >70% de novo native coronary stenoses requiring implantation of either a stent longer than 20 mm or of multiple overlapping stents. Exclusion criteria: Patients with saphenous graft lesion, bleeding diathesis, thrombocytopenia, history of stroke, active bleeding, severe uncontrolled hypertension, major surgery or trauma within 6 weeks. Mean age: 62 ys, male: 88%, diabetes: 27%, prior myocardial infarction: 67%. Acute Coronary Syndrome: 48% (Unstable angina: 48%, Non-STEMI: ?%, STEMI: 0%). ST-segment depression: ?%, CK-MB elevation: ?%, Troponin elevation: ?%. PCI: Atherectomy: 0%, Balloon angioplasty: 0%, Stent: 100%. Pre-treatment with clopidogrel: 0%, but 100% with ticlopidine.
Interventions	Abciximab (bolus of 0.25 mg/Kg, followed by an infusion of 0.125 µg/Kg/min for 12 hs) vs placebo. All patients treated with ASA and heparin. Ticlopidine 250 mg twice daily was started the day before the intervention and was prescribed to all patients for 4 weeks following the procedure.
Outcomes	Primary: safety (bleeding and vascular complications) and efficacy in reducing major in-hospital adverse cardiac events related to the procedure (death, MI and urgent revascularization) Secondary: reduction in death, MI, target lesion revascularization and angiographic binary restenosis at 6 months.
Notes	

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	By a "standard list of random numbers"
Allocation concealment?	Unclear	with the use of closed envelopes but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
Blinding? Primary	No	Open-label study.
Blinding? Secondary	No	Open-label study.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The study protocol is not available but the published reports include all expected outcomes.
Free of other bias?	No	The commercial name of the drug and the pharmaceutical company are listed in the Abstract.

TOPSTAR 2002

Methods	Method of treatment allocation: Not stated ("The patients were randomised by an independent study nurse"). Double-blinded?: Yes. Stratification: No. Placebo: Yes (0.9% NaCl solution). Sample size calculation: No. Intention-to-treat analysis: Not stated. Funding: Supported by a grant from MSD (Merck, Sharp and Dohme) GmbH, Germany. Follow-up: 30 days and 9 months.
Participants	Location: University of Würzburg, Würzburg, Germany. Eligibility criteria: 96 of 109 patients with stable CAD, a target lesion >70% suitable for PCI, and that underwent elective PCI after pretreatment with 375 mg of clopidogrel at least one day before PCI. Exclusion criteria: Acute coronary syndromes, stenosis located in venous or arterial bypass grafts; renal insufficiency; recent peptic ulcers or a history of bleeding, thrombocytopenia or thrombolytic therapy within the previous 24 hs; stroke during the past two years; severe hypertension; neoplasms; and previous or planned administration of a GP IIb/IIIa receptor antagonist. Mean age: 65 ys, male: 75%, prior myocardial infarction: 38%. Acute coronary syndrome: 0% ST-segment depression: ?, CK-MB elevation: ?, Troponin elevation: ?. PCI: Atherectomy: 0%, Balloon angioplasty: 8%, Stent: 92%. Pre-treatment with clopidogrel: 100%.
Interventions	Tirofiban bolus of 10 µg/Kg + infusion of 0.15 µg/Kg/min.
Outcomes	Primary: presence of post interventional release of troponin T after 24 hs. Secondary: incidence of death, MI or target vessel revascularization
Notes	All patients pre-treated with clopidogrel 375 mg and ASA 500 mg at least one day before PCI

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Not stated ("The patients were randomised by an independent study nurse").
Allocation concealment?	Unclear	Not stated ("The patients were randomised by an independent study nurse").
Blinding? Primary	No	Blinding of participants and key study personnel ensured during the study period (first 48 hs after PCI) but likely that the blinding could have been broken afterwards.
Blinding? Secondary	No	Blinding of participants and key study personnel ensured during the study period (first 48 hs after PCI) but likely that the blinding could have been broken afterwards.
Incomplete outcome data addressed? Primary	Yes	No missing outcome data.
Incomplete outcome data addressed? Secondary	Yes	No missing outcome data.
Free of selective reporting?	Yes	The study protocol is not available but the published reports include all expected outcomes.
Free of other bias?	Unclear	Funding: Supported by a grant from MSD (Merck, Sharp and Dohme) GmbH, Germany.

Footnotes

Characteristics of excluded studies

ACUITY 2006

Reason for exclusion	Comparison of unfractionated heparin or enoxaparin plus any GP IIb/IIIa inhibitor vs. bivalirudin plus any GP IIb/IIIa inhibitor vs. bivalirudin alone.

ADVANCE MI 2005

Reason for exclusion	Facilitated thrombolysis (eptifibatide + tenecteplase) vs. facilitated PCI (eptifibatide) in patients with STEMI

Alexander 1999

Reason for exclusion	Substudy of the PURSUIT trial on the effect of prior use of aspirin in GP IIb/IIIa inhibitors use in unstable angina

Batyraliev 2009

Reason for exclusion	Study on rescue coronary angioplasty after unsuccessful thombolysis

Bellandi 2006

Reason for exclusion	Comparison of Abciximab administered in the emergency room vs. in the catheterization laboratory

Bertrand 2006

Reason for exclusion	Study comparing bolus Abciximab versus Bolus + infusion Abciximab

Blankenship 1998

Reason for exclusion	EPIC sub study on local bleeding after GP IIb/IIIa inhibitors use

BOCHUM 2004

Reason for exclusion	Open-label pilot study to assess the practical application and safety of pre-hospital eptifibatide vs control in patients with suspected ACS. Patients were assigned eptifibatide or control in even/uneven days. Of the 356 patients included, only 42% had a NSTEACS, while 32% had a STEMI and 42% had a non specific chest pain.

Boehrer 1994

Reason for exclusion	EPIC substudy on the effect of abciximab in coronary artery bypass surgery

Brener 1999

Reason for exclusion	RAPPORT substudy on the pattern of reperfusion in myocardial infarction patients treated with abciximab

Cannon 1998

Reason for exclusion	Trial with an oral GP IIb/IIIa antagonist (TIMI 12)

Casserly 1998

Reason for exclusion	This is not a clinical trial but a case report

Claeys 2002

Reason for exclusion	Open-label, non-randomized study. Comparison of the degree of inhibition of platelet aggregation after the administration of a loading dose of clopidogrel vs. abciximab. Thirty-nine patients that underwent PCI with stent implantation

CLEAR PLATELETS 1b 2006

Reason for exclusion	Study on the effects of eptifibatide on top of aspirin and clopidogrel on platelet aggregation and clinical markers of inflammation and necrosis. No clinical endpoints reported.

CLOTILDA 2005

Reason for exclusion	Comparison of tirofiban vs. provisional abciximab.

Costantini 2004

Reason for exclusion	Substudy of the CADILLAC Trial

Cutlip 2003

Reason for exclusion	Tirofiban vs control in the emergency room followed by any IIb/IIIa inhibitor during PCI a median of 90 min later

De Luca 2005

Reason for exclusion	This is not a RCT but a descriptive study on the effects of abciximab in diabetic patients with or without metabolic control identified retrospectively

EARLY-ACS 2009

Reason for exclusion	Study comparing eptifibatide administered at admission versus at the catheterisation laboratory (a mean of 12 hs later) in 9492 patients with NSTEACS.

ELISA 2003

Reason for exclusion	The ELISA pilot study. This study compared two different strategies in patients with UA/NSTEMI rather than two different treatments: immediate (median 6 h) ICP after randomization without pre-treatment with tirofiban versus delayed (median 50 h) ICP after prolonged pre-treatment with tirofiban. Thus, although tirofiban administration was randomized the basal conditions were different because of differences in timing of administration

Ellis 2008

Reason for exclusion	RCT on facilitated PCI in patients with STEMI comparing PCI after abciximab plus half-dose reteplase vs. abciximab alone.

Emre 2006

Reason for exclusion	Comparison of tirofiban administered in the emergency room vs. in the catheterisation laboratory

ERAMI 2006

Reason for exclusion	Comparison of abciximab administered in the emergency room vs. in the catheterisation laboratory

Ercan 2004

Reason for exclusion	Small study looking at differences in CRP at 48-72 h. No clinical events reported.

EVEREST 2006

Reason for exclusion	Comparison of tirofiban administered in the CCU vs. in the catheterization laboratory

Ghaffari 1998

Reason for exclusion	EPILOG and EPIC joined subanalysis

GRAPE 1999

Reason for exclusion	Pilot study performed in 60 patients with STEMI treated with primary PCI without a control group. Not a randomized study

Gunasekara 2006

Reason for exclusion	A non-randomized comparison of abciximab vs. high-dose tirofiban

GUSTO V 2001

Reason for exclusion	Trial comparing the addition of a GP IIb/IIIa antagonist to the fibrinolytic treatment in patients with ST-segment elevation acute myocardial infarction

Hamm 1999

Reason for exclusion	Substudy of the CAPTURE trial. Differential effects of abciximab in patients with refractory angina according to basal troponin levels

Hanefeld 2002

Reason for exclusion	Pilot study of the BOCHUM trial

Heeschen 1999

Reason for exclusion	Substudy of the PRISM trial. Effects of tirofiban in patients with UA/NSTEMI according to baseline troponin levels

HORIZONS-AMI 2008

Reason for exclusion	RCT comparing Bivalirudin versus GP IIb/IIIa inhibitors (any) plus heparin in patients with STEMI submitted to primary PCI

IMPACT-AMI 1997

Reason for exclusion	RCT on the effect of GP IIb/IIIa inhibitors in patients with ST-segment elevation acute myocardial infarction treated with thrombolytics

INTAMI 2005

Reason for exclusion	Comparison of eptifibatide administered in the emergency room vs. in the cath lab in patients with STEMI submitted to primary PCI

Kereiakes 1997

Reason for exclusion	Oral GP IIb/IIIa inhibitor xemilofiban. It is not a randomized clinical trial.

Kereiakes 1998a

Reason for exclusion	Oral GP IIb/IIIa inhibitor xemilofiban

Kereiakes 1998b

Reason for exclusion	Substudy of the EPILOG trial. Subanalysis in unplanned stent patients

Kleiman 1998

Reason for exclusion	EPILOG subanalysis in patients with diabetes

Klootwijk 1998

Reason for exclusion	CAPTURE substudy on silent ischaemia in GP IIb/IIIa inhibitors in unstable angina.

Krause 1996

Reason for exclusion	Abstract from a Congress. A phase II RCT with 3 escalating doses of i.v. Fradafiban in 65 patients with stable angina submitted to elective PTCA. Aim: Safety and antiplatelet effects. No clinical events reported

Lefkovits 1996

Reason for exclusion	EPIC substudy on the effects of abciximab on outcomes after percutaneous transluminal coronary angioplasty for acute myocardial infarction

Lenderink 2003

Reason for exclusion	Substudy of the CAPTURE trial

Lincoff 1997

Reason for exclusion	EPIC substudy of prevention of ischaemic complications in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty

Mahaffey 1999

Reason for exclusion	PURSUIT Substudy on stroke after GP IIb/IIIa inhibitors in unstable angina.

Mak 1997

Reason for exclusion	EPIC non-randomized substudy on distal embolization during coronary artery bypass surgery

McClure 1999

Reason for exclusion	PURSUIT substudy on the significance of thrombocitopenia after non-ST-elevation in acute coronary syndromes

McElwee 1997

Reason for exclusion	Cost effectiveness analysis review

Miller 1999

Reason for exclusion	Non-randomized GUSTO-III trial subanalysis on effectiveness of GP IIb/IIIa inhibitors in patients in whom thrombolysis failed.

Mockel 2005

Reason for exclusion	Comparison of prehospital tirofiban versus fibrinolysis before direct PCI in patients with STEMI

Morrow 2001

Reason for exclusion	Substudy of the TACTICS trial

Muller 1997

Reason for exclusion	Analysis of the degree of platelet inhibition by an oral GP IIb/IIIa inhibitor fradafiban (ledrafiban is the active prodrug). Not a randomized clinical trial

Murdock 1997

Reason for exclusion	Non-randomized study of patients with ST segment elevation acute myocardial infarction treated with GP IIb/IIIa inhibitors

Narins 1999

Reason for exclusion	EPIC subanalysis on periprocedural myocardial infarction during percutaneous transluminal coronary angioplasty

Neumann 1998

Reason for exclusion	Substudy on coronary flow and left ventricular ejection fraction after GP IIb/IIIa inhibitors in patients with ST-segment elevation acute myocardial infarction who underwent stent implantation.

Newby 1999

Reason for exclusion	Design description of the SYMPHONY trial with oral GP IIb/IIIa inhibitor sibrafiban

Newby 2001

Reason for exclusion	A substudy of the PARAGON-B study

Okmen 2006

Reason for exclusion	Comparison of tirofiban vs no tirofiban on QT dispersion in patients that underwent PCI. Pateints with failed PCI were excluded (?) and no clinical outcomes were reported

On-TIME 2004

Reason for exclusion	Pre-hospital tirofiban vs hospital (median delay 59 m) tirofiban during primary PCI in patients with ST-segment elevation acute myocardial infarction

PARADIGM 1998

Reason for exclusion	Trial on GP IIb/IIIa blockers in patients with ST-segment elevation acute myocardial infarction treated with thrombolytics

PARAGON-B 2001

Reason for exclusion	PARAGON-B substudy on the effects of lamifiban according to baseline troponin levels.

Pels 2008

Reason for exclusion	Abciximab administered in the ambulance versus in the catheterisation laboratory in patients with ST-segment elevation myocardial infarction undergoing primary PCI

Petronio 2002

Reason for exclusion	Rescue PCI in STEMI after thrombolysis

Prati 2005

Reason for exclusion	Small study on the effects of abciximab on coronary microcirculation

PROLOG 1997

Reason for exclusion	Study on the effect of different doses of heparin in patients treated with abciximab during percutaneous revascularization

Rakowski 2007

Reason for exclusion	Abciximab administered in the emergency room versus in the catheterisation laboratory in patients with ST segment elevation myocardial infarction undergoing primary PCI. No clinical outcomes were reported.

RELAx-AMI 2007

Reason for exclusion	Abciximab administered in the emergency room versus in the catheterisation laboratory in patients with ST segment elevation myocardial infarction undergoing primary PCI

ReoPro-BRIDGING 2004

Reason for exclusion	Abciximab at admission versus abciximab immediately before primary PCI (mean difference 62 min) in patients with ST segment elevation myocardial infarction

REPLACE-2 2003

Reason for exclusion	A comparison of bivalirudin plus any GP IIb/IIIa inhibitor on a provisional basis for complications during PCI, with heparin plus planned treatment with any GP IIb/IIIa inhibitor

Roe 2003

Reason for exclusion	Treatment with eptifibatide vs placebo in the emergency department followed by open-label eptifibatide 12-24 h later.

Shen 2007

Reason for exclusion	RCT comparing Tirofiban vs. Control in 160 patients with STEMI, and performed during the same dates that the Shen 2008 study performed with the same drug and the same type of patients. The authors were contacted to clarify if one study include the patients of the other study. Since they have not respond, the study was excluded from the review.

Simpfendorfer 1997

Reason for exclusion	Controlled clinical trial with oral GP IIb/IIIa blockade with xemilofiban in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty.

SPEED P-St 2000

Reason for exclusion	Primary PCI with or without GP IIb/IIIa antagonist in patients with ST-segment elevation acute myocardial infarction treated with a thrombolytic (facilitated PCI).

Steen 2005

Reason for exclusion	Comparison of myocardial tissue perfusion with and without Tirofiban in patients with STEMI. No clinical events reported.

STOPAMI 2000

Reason for exclusion	Primary PCI with stent and abciximab vs. thrombolysis in patients with STEMI

STOPAMI-2 2002

Reason for exclusion	Controlled clinical trial with GP IIb/IIIa blockade in patients with ST-segment elevation acute myocardial infarction, comparing primary PCI with stenting and abciximab versus fibrinolysis and abciximab. No comparison was performed between abciximab and placebo or control.

Svensson 2006

Reason for exclusion	Thrombolysis vs facilitated PCI with abciximab in patients with STEMI

SYMPHONY 2 2001

Reason for exclusion	Controlled clinical trial with oral GP IIb/IIIa blockade with sibrafiban in patients with acute coronary syndromes 7 days or more after admission.

TAMI-8 1993

Reason for exclusion	Pilot study on the effects of abciximab in patients with STEMI treated with thrombolytics

TARGET 2001

Reason for exclusion	RCT comparing abciximab with tirofiban in patients submitted to PCI

Thiele 2005

Reason for exclusion	Patients with STEMI were randomized to either pre-hospital facilitated fibrinolysis (half-dose reteplase+abciximab) or pre-hospital facilitated fibrinolysis (half-dose reteplase+abciximab) plus PCI

TIGER-PA 2003

Reason for exclusion	Open-label randomization of patients (n=100) with ST segment elevation MI to "early" administration of Tirofiban in the emergency room versus "late" administration in the catheterization laboratory immediately before primary PCI.

TIMI 14 1999

Reason for exclusion	Thrombolysis with or without abciximab in patients with STEMI

TIMI 15A 2000

Reason for exclusion	A randomized open-label study of a new drug administered i.v. for 24 to 96 h in 91 patients. Patients were assigned to 1 of 9 regimens of RPR 109891. No Placebo group was included

TITAN-TIMI 34 2006

Reason for exclusion	Comparison on the administration of Eptifibatide in the emergency room versus provisional eptifibatide in the catheterisation laboratory

Valgimigli 2005

Reason for exclusion	Comparison of tirofiban and an eluting stent vs. Abciximab + bare metal stent during primary PCI in patients with STEMI

van den Brand 1999

Reason for exclusion	CAPTURE substudy on angiographic assessment of GPIIb/IIIa inhibitor use.

van den Merkhof 1999

Reason for exclusion	Study on the TIMI perfusion grade of 60 patients with STEMI treated with abciximab in the emergency department. Not a RCT

Wong 2003

Reason for exclusion	Small study (n=32) on the coronary flow reserve before and after stenting in patients receiving tirofiban vs. control. No data on clinical events

Zajdel 2002

Reason for exclusion	Abstract from a congress, written in polish, with preliminary data. No clinical events.

Zhao 1999

Reason for exclusion	PRISM plus substudy on angiographic results with tirofiban

Footnotes

Characteristics of studies awaiting classification

Gasior 2003

Methods	
Participants	
Interventions	
Outcomes	
Notes	We were unable to obtain a copy of this paper for this review update. Further efforts to retrieve it will commence for next update.

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

1 Summary assessment of the risk of bias (allocation concealment and blinding) for major endpoints within and across studies on initial treatment of patients with NSTEACS

Study	N	30-day mortality	6-month mortality	30-day death or MI	6-month death or MI	Major bleeding	Within study
CANADIAN 1996	365	Low	NA	Low	NA	Low	Low
Schulman 1996	227	Low	NA	Low	NA	Low	Low
PURSUIT 1998	10948	Low	Low	Low	Low	Low	Low
PRISM 1998	3232	Low	NA	Low	NA	Low	Low
PARAGON A 1998	2282	Low	Low	Low	Low	Low	Low
PRISM Plus 1998	1915	Low	Low	Low	Low	Low	Low
GUSTO-IV 2001	7800	Low	NA	Low	NA	Low	Low
PARAGON B 2002	5225	Low	NA	Low	NA	Low	Low
ELISA-2 2006	328	Low	NA	High	NA	High	High
PRACTICE 2007	393	Low	Low	Low	Low	Low	Low
ACROSS STUDIES	31069	Low	Low	Low	Low	Low	

Footnotes

Allocation concealment and blinding were the 2 selected key domains.

Bias for each endpoint: NA: Not applicable; Low: Plausible bias unlikely to seriously alter the results; Unclear:

Plausible bias that raises some doubt about the results; High: Plausible bias that seriously weakens confidence in the results.

Bias within a study: Low: Low risk of bias for all key domains; Unclear: Unclear risk of bias for one or more key domains; High: High risk of bias for one or more key domains.

Bias across studies: Low: Most information is from studies at low risk of bias; Unclear: Most information is from studies at low or unclear risk of bias; High: The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of the results.

2 Summary assessment of the risk of bias (allocation concealment and blinding) for major endpoints within and across PCI studies

Study	N	30-day mortality	6-month mortality	30-day death or MI	6-month death or MI	Major Bleeding	Within study
EPIC 1994	2099	Low	Low	Low	Low	Low	Low
Simoons 1994	60	Low	NA	Low	NA	Low	Low
IMPACT 1995	150	Low	NA	Low	NA	Unclear	Unclear
Kereiakes 1996	93	Low	NA	Low	NA	Low	Low
RESTORE 1997	2141	Low	Low	Low	Low	Low	Low
IMPACT-II 1997	4010	Low	NA	Low	NA	Low	Low
EPILOG 1997	2792	Low	Low	Low	Low	Low	Low
CAPTURE 1997	1265	Low	Low	Low	Low	Low	Low
EPISTENT 1998	2399	Low	Low	Low	Low	Low	Low
RAPPORT 1998	483	Low	Low	Low	Low	Low	Low
ERASER 1999	215	Low	Low	Low	Low	Low	Low
Galassi 1999	106	High	NA	High	NA	High	High
Chen 2000	42	Unclear	NA	Unclear	NA	Unclear	Unclear
ESPRIT 2000	2064	Low	Low	Low	Low	Low	Low
ISAR-2 2000	401	Unclear	NA	High	NA	High	High
PRIDE 2001	127	Unclear	NA	Unclear	NA	Unclear	Unclear
ADMIRAL 2001	300	Low	Low	Unclear	Unclear	Unclear	Unclear
Tamburino 2002	107	High	High	High	High	High	High
TOPSTAR 2002	96	Low	Low	Unclear	Unclear	Unclear	Unclear
Juergens 2002	894	Low	Low	Low	Unclear	Unclear	Unclear
ACE 2003	400	High	High	High	High	High	High
CADILLAC 2003	2082	Low	Low	High	High	High	High
ADVANCE 2004	202	Low	Low	Unclear	Unclear	Unclear	Unclear
ISAR SMART-2 2004	502	NA	Low	NA	Low	Low	Low
ISAR-REACT 2004	2159	Low	Low	Low	Low	Low	Low
ISAR-SWEET 2004	701	Low	Low	Low	Low	Low	Low
Claeys 2005	200	Unclear	Unclear	High	High	High	High
ASIAD 2005	254	Low	Low	Unclear	Unclear	Unclear	Unclear
ISAR-REACT 2 2006	2022	Low	Low	Low	Low	Low	Low
FU 2008	150	NA	Unclear	NA	Unclear	Unclear	Unclear
Cuisset 2008	149	Low	NA	High	NA	High	High
Shen 2008	172	Unclear	Unclear	High	High	High	High
On-TIME 2 2008	984	Low	NA	Low	NA	Low	Low
OPTIMIZE-IT 2009	46	Low	Low	High	High	High	High
JEPPORT 2009	973	Low	NA	Low	NA	Low	Low
CLEAR PLATELETS-2 2009	200	Low	Low	High	High	High	High
BRAVE-3 2009	800	Low	NA	Low	NA	Low	Low
3T/2R 2009	263	Low	NA	Low	NA	Low	Low
ACROSS STUDIES	31020	Low	Low	Unclear	Unclear	Unclear	

Footnotes

Allocation concealment and blinding were the 2 selected key domains.

Bias for each endpoint: NA: Not applicable; Low: Plausible bias unlikely to seriously alter the results; Unclear: Plausible bias that raises some doubt about the results; High: Plausible bias that seriously weakens confidence in the results.

Bias within a study: Low: Low risk of bias for all key domains; Unclear: Unclear risk of bias for one or more key domains; High: High risk of bias for one or more key domains.

Bias across studies: Low: Most information is from studies at low risk of bias; Unclear: Most information is from studies at low or unclear risk of bias; High: The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of the results.

3 Main results for the primary outcomes

Intervention	30-day mortality	6-month mortality	30-day death or non-fatal MI	6-month death or non-fatal MI
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1. During PCI (all patients)	0.76 (0.62, 0.95)	0.84 (0.71, 1.00)	0.65 (0.60, 0.72)	0.70 (0.61, 0.81)
1.1. Subgroup analysis by patient's condition				
Patients with stable CAD	0.69 (0.32, 1.47)	0.83 (0.59, 1.17)	0.68 (0.55, 0.85)	0.76 (0.63, 0.92)
Patients with NSTEACS	0.79 (0.47, 1.32)	1.04 (0.76, 1.43)	0.68 (0.56, 0.83)	0.79 (0.66, 0.94)
Primary PCI in patients with STEMI	0.83 (0.60, 1.16)	0.72 (0.53, 0.99)	0.74 (0.57, 0.95)	0.57 (0.35, 0.93)
1.2. Subgroup analysis by technique				
Balloon angioplasty	0.79 (0.55, 1.14)	1.06 (0.75, 1.50)	0.65 (0.56, 0.75)	0.78 (0.65, 0.94)
PCI with stent placement	0.73 (0.54, 0.98)	0.77 (0.62, 0.96)	0.65 (0.57, 0.74)	0.67 (0.59, 0.76)
1.3. Subgroup analysis by pre-treatment with clopidogrel	0.83 (0.56, 1.22)	0.92 (0.70, 1.21)	0.80 (0.66, 0.96)	0.80 (0.67, 0.95)
Patients with ACS	0.80 (0.53, 1.22)	0.93 (0.63, 1.38)	0.73 (0.58, 0.92)	0.69 (0.54, 0.89)
Patients without ACS	1.00 (0.32, 3.11)	0.91 (0.62, 1.33)	0.97 (0.70, 1.35)	0.92 (0.72, 1.18)
2. As initial medical treatment of NSTEACS	0.91 (0.80, 1.03)	1.00 (0.87, 1.15)	0.92 (0.86, 0.99)	0.88 (0.81, 0.96)

MI, myocardial infarction; PCI, percutaneous coronary intervention; CAD, coronary artery disease; NSTEACS, non-ST segment elevation acute coronary syndrome; STEMI, ST-segment elevation acute myocardial infarction. ACS, Acute Coronary Syndromes

Footnotes

4 Main results for the secondary outcomes

Intervention	30-day urgent revasc	6-month revasc	30-day death, MI or revasc	6-month death, MI or revasc
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1. During PCI (all patients)	0.61 (0.53, 0.70)	0.86 (0.79, 0.94)	0.64 (0.57, 0.73)	0.78 (0.71, 0.87)
1.1. Subgroup analysis by patient's condition				
Patients with stable CAD	0.84 (0.54, 1.32)	0.93 (0.80, 1.07)	0.68 (0.45, 1.04)	0.86 (0.76, 0.98)
Patients with NSTEACS	0.70 (0.53, 0.93)	0.92 (0.79, 1.06)	0.70 (0.59, 0.84)	0.86 (0.76, 0.97)
Primary PCI in patients with STEMI	0.56 (0.40, 0.77)	0.75 (0.61, 0.93)	0.64 (0.52, 0.80)	0.80 (0.68, 0.94)
1.2. Subgroup analysis by technique				
Balloon angioplasty	0.58 (0.49, 0.70)	0.81 (0.60, 1.10)	0.63 (0.51, 0.76)	0.84 (0.75, 0.94)
PCI with stent placement	0.71 (0.55, 0.93)	0.88 (0.79, 0.98)	0.66 (0.55, 0.80)	0.73 [0.63, 0.85)
1.3. Subgroup analysis by pre-treatment with clopidogrel	0.85 (0.60, 1.21)	0.90 (0.79, 1.03)	0.81 (0.68, 0.97)	0.87 (0.77, 0.97)
Patients with ACS	0.77 (0.51, 1.14)	0.78 (0.62, 0.99)	0.74 (0.60, 0.92)	0.74 (0.61, 0.89)
Patients without ACS	1.24 (0.59, 2.62)	0.97 (0.82, 1.13)	1.01 (0.73, 1.40)	0.95 (0.82, 1.10)
revasc, revascularization; MI, myocardial infarction; PCI, percutaneous coronary intervention; CAD, coronary artery disease; NSTEACS, non-ST segment elevation acute coronary syndrome; STEMI, ST segment elevation myocardial infarction. ACS, Acute Coronary Syndromes.				

Footnotes

5 Main results for safety outcomes

Intervention	30-day major bleeding (OR, 95% CI)
1. PCI (all patients)	1.38 (1.20 to 1.60)
1.1. Subgroup analysis by patient's condition	
Patients with stable CAD	1.86 (1.11 to 3.12)
Patients with NSTEACS	1.41 (1.03 to 1.93)
Primary PCI in patients with STEMI	1.49 (1.06 to 2.11)
1.2. Subgroup analysis by technique	
Balloon angioplasty	1.38 (1.02 to 1.86)
PCI with stent placement	1.33 (0.99 to 1.80)
1.3. Subgroup analysis by pre-treatment with clopidogrel	1.31 (0.91 to 1.90)
Patients with ACS	1.16 (0.74 to 1.82)
Patients without ACS	1.68 (0.88 to 3.20)
2. As initial medical treatment of patients with NSTEACS	1.27 (1.12, 1.43)
d, day; PCI, percutaneous coronary intervention; NSTEACS, non-ST elevation acute coronary syndrome; STEMI, ST elevation myocardial infarction; CAD, coronary artery disease	

Footnotes

References to studies

Included studies

3T/2R 2009

* Valgimigli M, Campo G, de Cesare N, Meliga E, Vranckx P, Furgieri A, et al. Intensifying platelet inhibition with tirofiban in poor responders to aspirin, clopidogrel, or both agents undergoing elective coronary intervention: results from the double-blind, prospective, randomized Tailoring Treatment with Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel study. Circulation 2009;119(25):3215-22.

Valgimigli M, Campo G, de Cesare N, Vranckx P, Hamon M, Angiolillo DJ, et al. Tailoring treatment with tirofiban in patients showing resistance to aspirin and/or resistance to clopidogrel (3T/2R). Rationale for the study and protocol design. Cardiovascular Drugs and Therapy 2008;22(4):313-20.

ACE 2003

Antoniucci D, Migliorini A, Parodi G, Valenti R, Rodriguez A, Hempel A, et al. Abciximab-supported infarct artery stent implantation for acute myocardial infarction and long-term survival: a prospective, multicenter, randomized trial comparing infarct artery stenting plus abciximab with stenting alone. Circulation 2004;109(14):1704-6.

* Antoniucci D, Rodriguez A, Hempel A, Valenti R, Migliorini A, Vigo F, et al. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. Journal of the American College of Cardiology 2003;42:1879-85.

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Other published versions of this review

Classification pending references

Data and analyses

1 During PCI (all patients)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 30-day mortality	36	30696	Odds Ratio (M-H , Fixed , 95% CI)	0.76 [0.62, 0.95]
1.1.1 Blinded studies with a placebo group	26	26833	Odds Ratio (M-H , Fixed , 95% CI)	0.78 [0.61, 1.00]
1.1.2 No blinded studies and without placebo	10	3863	Odds Ratio (M-H , Fixed , 95% CI)	0.72 [0.47, 1.12]

1.2 6-month mortality	24	22364	Odds Ratio (M-H , Fixed , 95% CI)	0.84 [0.71, 1.00]
1.2.1 Blinded studies with a placebo group	17	19157	Odds Ratio (M-H , Fixed , 95% CI)	0.85 [0.71, 1.03]
1.2.2 No blinded studies and without placebo	7	3207	Odds Ratio (M-H , Fixed , 95% CI)	0.80 [0.56, 1.14]
1.3 30-day mortality or myocardial infarction	36	30696	Odds Ratio (M-H , Fixed , 95% CI)	0.65 [0.60, 0.72]
1.3.1 Blinded studies with a placebo group	26	26833	Odds Ratio (M-H , Fixed , 95% CI)	0.67 [0.60, 0.73]
1.3.2 No blinded studies and without placebo	10	3863	Odds Ratio (M-H , Fixed , 95% CI)	0.55 [0.40, 0.76]
1.4 6-month mortality or myocardial infarction	24	22866	Odds Ratio (M-H , Random , 95% CI)	0.70 [0.61, 0.81]
1.4.1 Blinded studies with a placebo group	17	19157	Odds Ratio (M-H , Random , 95% CI)	0.70 [0.61, 0.80]
1.4.2 No blinded studies and without placebo	8	3709	Odds Ratio (M-H , Random , 95% CI)	0.63 [0.40, 1.01]
1.5 30-day urgent revascularisation	35	30433	Odds Ratio (M-H , Fixed , 95% CI)	0.61 [0.53, 0.70]
1.6 6-month urgent revascularisation	22	19476	Odds Ratio (M-H , Fixed , 95% CI)	0.86 [0.79, 0.94]
1.7 30-day mortality, myocardial infarction or urgent revascularisation	35	30433	Odds Ratio (M-H , Random , 95% CI)	0.64 [0.57, 0.73]
1.8 6-month mortality, myocardial infarction or urgent revascularisation	23	20360	Odds Ratio (M-H , Random , 95% CI)	0.78 [0.71, 0.87]
1.9 30-day major bleeding	35	30528	Odds Ratio (M-H , Fixed , 95% CI)	1.38 [1.20, 1.60]
1.9.1 Blinded studies with a placebo group	25	26665	Odds Ratio (M-H , Fixed , 95% CI)	1.38 [1.19, 1.61]
1.9.2 No blinded studies and without placebo	10	3863	Odds Ratio (M-H , Fixed , 95% CI)	1.42 [0.83, 2.42]

2 Subgroup of PCI stable coronary patients

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 30-day mortality	12	6152	Odds Ratio (M-H , Fixed , 95% CI)	0.69 [0.32, 1.47]
2.2 6-month mortality	8	5968	Odds Ratio (M-H , Fixed , 95% CI)	0.83 [0.59, 1.17]
2.3 30-day mortality or myocardial infarction	12	6152	Odds Ratio (M-H , Fixed , 95% CI)	0.68 [0.55, 0.85]
2.4 6-month mortality or myocardial infarction	8	5968	Odds Ratio (M-H , Fixed , 95% CI)	0.76 [0.63, 0.92]
2.5 30-day urgent revascularisation	11	5889	Odds Ratio (M-H , Fixed , 95% CI)	0.84 [0.54, 1.32]
2.6 6-month urgent revascularisation	8	5968	Odds Ratio (M-H , Fixed , 95% CI)	0.93 [0.80, 1.07]
2.7 30-day mortality, myocardial infarction or urgent revascularisation	11	5889	Odds Ratio (M-H , Random , 95% CI)	0.68 [0.45, 1.04]
2.8 6-month mortality, myocardial infarction or urgent revascularisation	8	5968	Odds Ratio (M-H , Fixed , 95% CI)	0.86 [0.76, 0.98]
2.9 30-day major bleeding	12	6152	Odds Ratio (M-H , Fixed , 95% CI)	1.86 [1.11, 3.12]

3 Subgroup of PCI patients with NSTEACS

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

3.1 30-day mortality	4	5488	Odds Ratio (M-H , Fixed , 95% CI)	0.79 [0.47, 1.32]
3.2 6-month mortality	3	5426	Odds Ratio (M-H , Fixed , 95% CI)	1.04 [0.76, 1.43]
3.3 30-day mortality or myocardial infarction	4	5488	Odds Ratio (M-H , Fixed , 95% CI)	0.68 [0.56, 0.83]
3.4 6-month mortality or myocardial infarction	3	5426	Odds Ratio (M-H , Fixed , 95% CI)	0.79 [0.66, 0.94]
3.5 30-day urgent revascularisation	4	5488	Odds Ratio (M-H , Fixed , 95% CI)	0.70 [0.53, 0.93]
3.6 6-month urgent revascularisation	3	5426	Odds Ratio (M-H , Fixed , 95% CI)	0.92 [0.79, 1.06]
3.7 30-day mortality, myocardial infarction or urgent revascularisation	4	5488	Odds Ratio (M-H , Fixed , 95% CI)	0.70 [0.59, 0.84]
3.8 6-month mortality, myocardial infarction or urgent revascularisation	3	5426	Odds Ratio (M-H , Fixed , 95% CI)	0.86 [0.76, 0.97]
3.9 30-day major bleeding	4	5488	Odds Ratio (M-H , Fixed , 95% CI)	1.41 [1.03, 1.93]

4 Subgroup of primary PCI in patients with ST segment elevation acute myocardial infarction

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 30-day mortality	8	6125	Odds Ratio (M-H , Fixed , 95% CI)	0.83 [0.60, 1.16]
4.2 6-month mortality	6	3587	Odds Ratio (M-H , Fixed , 95% CI)	0.72 [0.53, 0.99]
4.3 30-day mortality or myocardial infarction	8	6125	Odds Ratio (M-H , Fixed , 95% CI)	0.74 [0.57, 0.95]
4.4 6-month mortality or myocardial infarction	6	3587	Odds Ratio (M-H , Random , 95% CI)	0.57 [0.35, 0.93]
4.5 30-day urgent revascularisation	8	6125	Odds Ratio (M-H , Fixed , 95% CI)	0.56 [0.40, 0.77]
4.6 6-month urgent revascularisation	6	3587	Odds Ratio (M-H , Fixed , 95% CI)	0.75 [0.61, 0.93]
4.7 30-day mortality, myocardial infarction or urgent revascularisation	8	6125	Odds Ratio (M-H , Fixed , 95% CI)	0.64 [0.52, 0.80]
4.8 6-month mortality, myocardial infarction or urgent revascularisation	6	4375	Odds Ratio (M-H , Fixed , 95% CI)	0.80 [0.68, 0.94]
4.9 30-day major bleeding	9	6275	Odds Ratio (M-H , Fixed , 95% CI)	1.49 [1.06, 2.11]

5 Subgroup of balloon angioplasty

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 30-day mortality	11	13378	Odds Ratio (M-H , Fixed , 95% CI)	0.79 [0.55, 1.14]
5.2 6-month mortality	4	5291	Odds Ratio (M-H , Fixed , 95% CI)	1.06 [0.75, 1.50]
5.3 30-day mortality or myocardial infarction	11	13378	Odds Ratio (M-H , Fixed , 95% CI)	0.65 [0.56, 0.75]
5.4 6-month mortality or myocardial infarction	4	5291	Odds Ratio (M-H , Fixed , 95% CI)	0.78 [0.65, 0.94]
5.5 30-day urgent revascularisation	11	13378	Odds Ratio (M-H , Fixed , 95% CI)	0.58 [0.49, 0.70]
5.6 6-month urgent revascularisation	4	5291	Odds Ratio (M-H , Random , 95% CI)	0.81 [0.60, 1.10]

5.7 30-day mortality, myocardial infarction or urgent revascularisation	11	13378	Odds Ratio (M-H , Random , 95% CI)	0.63 [0.51, 0.76]
5.8 6-month mortality, myocardial infarction or urgent revascularisation	5	6229	Odds Ratio (M-H , Fixed , 95% CI)	0.84 [0.75, 0.94]
5.9 30-day major bleeding	10	13285	Odds Ratio (M-H , Random , 95% CI)	1.38 [1.02, 1.86]

6 Subgroup of stent implantation

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 30-day mortality	23	15110	Odds Ratio (M-H , Fixed , 95% CI)	0.73 [0.54, 0.98]
6.2 6-month mortality	17	12049	Odds Ratio (M-H , Fixed , 95% CI)	0.77 [0.62, 0.96]
6.3 30-day mortality or myocardial infarction	23	15110	Odds Ratio (M-H , Fixed , 95% CI)	0.65 [0.57, 0.74]
6.4 6-month mortality or myocardial infarction	17	12049	Odds Ratio (M-H , Fixed , 95% CI)	0.67 [0.59, 0.76]
6.5 30-day urgent revascularisation	22	14847	Odds Ratio (M-H , Fixed , 95% CI)	0.71 [0.55, 0.93]
6.6 6-month urgent revascularisation	16	11953	Odds Ratio (M-H , Fixed , 95% CI)	0.88 [0.79, 0.98]
6.7 30-day mortality, myocardial infarction or urgent revascularisation	22	14847	Odds Ratio (M-H , Random , 95% CI)	0.66 [0.55, 0.80]
6.8 6-month mortality, myocardial infarction or urgent revascularisation	17	12048	Odds Ratio (M-H , Random , 95% CI)	0.73 [0.63, 0.85]
6.9 30-day major bleeding	22	14885	Odds Ratio (M-H , Fixed , 95% CI)	1.33 [0.99, 1.80]

7 Subgroup of PCI patients pre-treated with clopidogrel

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 30-day mortality	10	7556	Odds Ratio (M-H , Fixed , 95% CI)	0.83 [0.56, 1.22]
7.1.1 Patients with ACS	5	4146	Odds Ratio (M-H , Fixed , 95% CI)	0.80 [0.53, 1.22]
7.1.2 Patients without ACS	5	3410	Odds Ratio (M-H , Fixed , 95% CI)	1.00 [0.32, 3.11]
7.2 6-month mortality	9	6308	Odds Ratio (M-H , Fixed , 95% CI)	0.92 [0.70, 1.21]
7.2.1 Patients with ACS	3	2396	Odds Ratio (M-H , Fixed , 95% CI)	0.93 [0.63, 1.38]
7.2.2 Patients without ACS	6	3912	Odds Ratio (M-H , Fixed , 95% CI)	0.91 [0.62, 1.33]
7.3 30-day mortality or myocardial infarction	10	7556	Odds Ratio (M-H , Fixed , 95% CI)	0.80 [0.66, 0.96]
7.3.1 Patients with ACS	5	4146	Odds Ratio (M-H , Fixed , 95% CI)	0.73 [0.58, 0.92]
7.3.2 Patients without ACS	5	3410	Odds Ratio (M-H , Fixed , 95% CI)	0.97 [0.70, 1.35]
7.4 6-month mortality or myocardial infarction	9	6308	Odds Ratio (M-H , Fixed , 95% CI)	0.80 [0.67, 0.95]
7.4.1 Patients with ACS	3	2396	Odds Ratio (M-H , Fixed , 95% CI)	0.69 [0.54, 0.89]
7.4.2 Patients without ACS	6	3912	Odds Ratio (M-H , Fixed , 95% CI)	0.92 [0.72, 1.18]

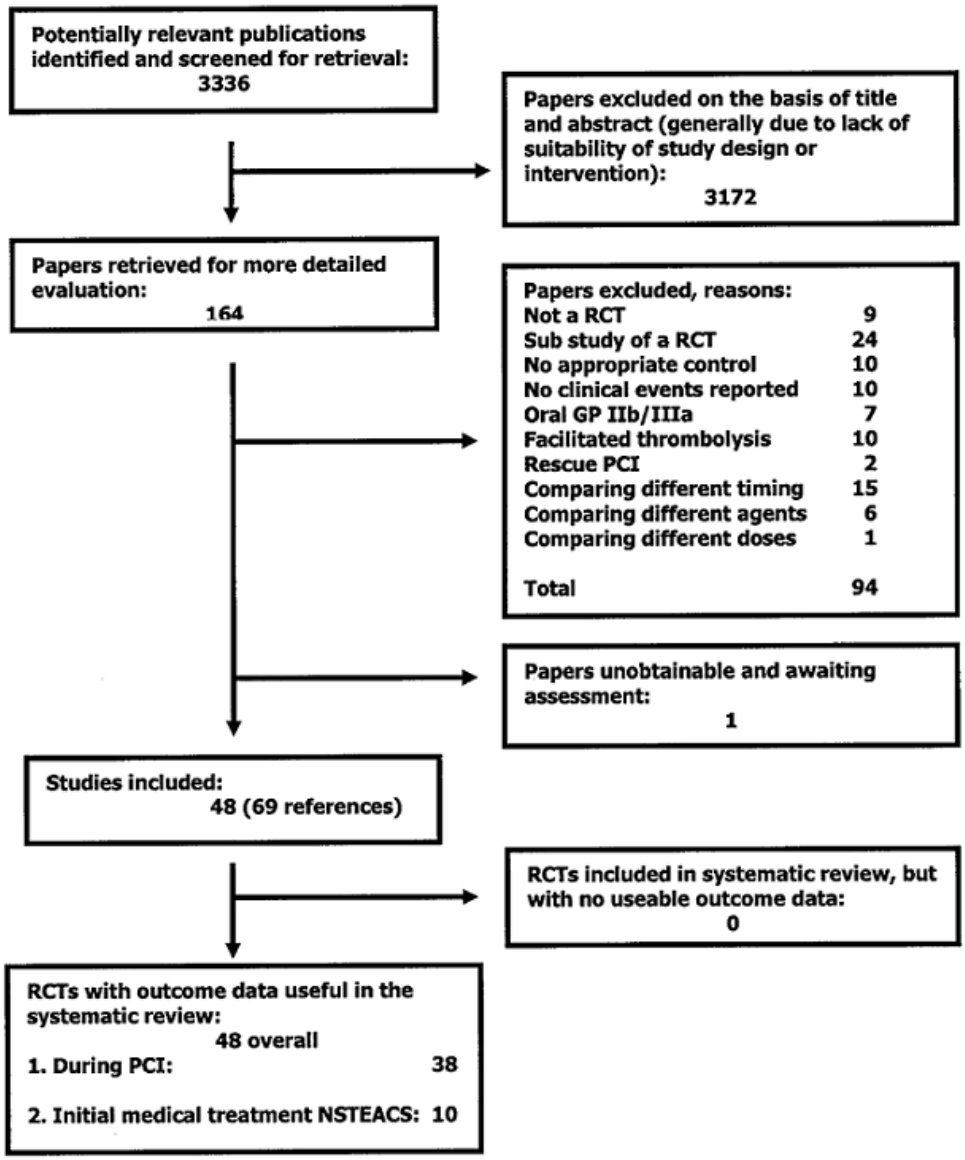
7.5 30-day urgent revascularisation	10	7556	Odds Ratio (M-H , Fixed , 95% CI)	0.85 [0.60, 1.21]
7.5.1 Patients with ACS	5	4146	Odds Ratio (M-H , Fixed , 95% CI)	0.77 [0.51, 1.14]
7.5.2 Patients without ACS	5	3410	Odds Ratio (M-H , Fixed , 95% CI)	1.24 [0.59, 2.62]
7.6 6-month urgent revascularisation	8	6212	Odds Ratio (M-H , Fixed , 95% CI)	0.90 [0.79, 1.03]
7.6.1 Patients with ACS	3	2396	Odds Ratio (M-H , Fixed , 95% CI)	0.78 [0.62, 0.99]
7.6.2 Patients without ACS	5	3816	Odds Ratio (M-H , Fixed , 95% CI)	0.97 [0.82, 1.13]
7.7 30-day mortality, myocardial infarction or urgent revascularisation	10	7556	Odds Ratio (M-H , Fixed , 95% CI)	0.81 [0.68, 0.97]
7.7.1 Patients with ACS	5	4146	Odds Ratio (M-H , Fixed , 95% CI)	0.74 [0.60, 0.92]
7.7.2 Patients without ACS	5	3410	Odds Ratio (M-H , Fixed , 95% CI)	1.01 [0.73, 1.40]
7.8 6-month mortality, myocardial infarction or urgent revascularisation	9	6308	Odds Ratio (M-H , Fixed , 95% CI)	0.87 [0.77, 0.97]
7.8.1 Patients with ACS	3	2396	Odds Ratio (M-H , Fixed , 95% CI)	0.74 [0.61, 0.89]
7.8.2 Patients without ACS	6	3912	Odds Ratio (M-H , Fixed , 95% CI)	0.95 [0.82, 1.10]
7.9 30-day major bleeding	10	7556	Odds Ratio (M-H , Fixed , 95% CI)	1.31 [0.91, 1.90]
7.9.1 Patients with ACS	5	4146	Odds Ratio (M-H , Fixed , 95% CI)	1.16 [0.74, 1.82]
7.9.2 Patients without ACS	5	3410	Odds Ratio (M-H , Fixed , 95% CI)	1.68 [0.88, 3.20]

8 As initial medical treatment in patients with NSTEACS

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
8.1 30-day mortality	10	31069	Odds Ratio (M-H , Fixed , 95% CI)	0.91 [0.80, 1.03]
8.2 6-month mortality	4	14051	Odds Ratio (M-H , Fixed , 95% CI)	1.00 [0.87, 1.15]
8.3 30-day mortality or myocardial infarction	10	31069	Odds Ratio (M-H , Fixed , 95% CI)	0.92 [0.86, 0.99]
8.4 6-month mortality or myocardial infarction	5	19276	Odds Ratio (M-H , Fixed , 95% CI)	0.88 [0.81, 0.96]
8.5 30-day major bleeding	10	30638	Odds Ratio (M-H , Fixed , 95% CI)	1.27 [1.12, 1.43]

Figures

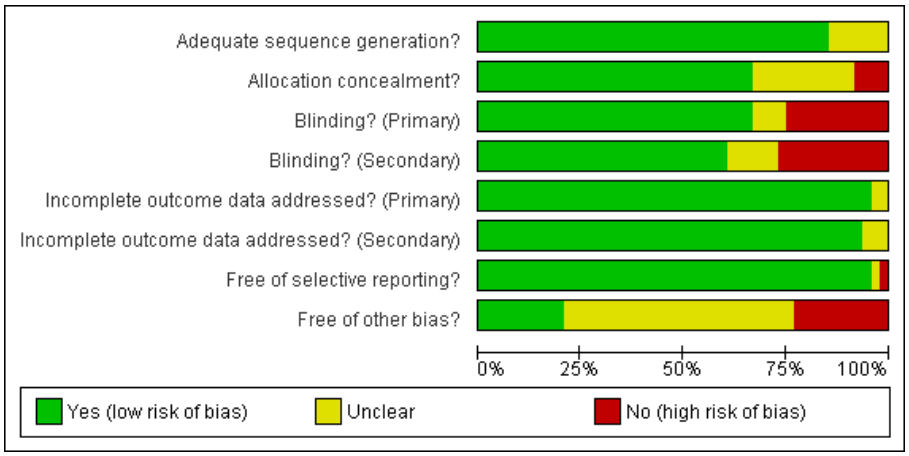
Figure 1



Caption

QUOROM flow chart of study selection

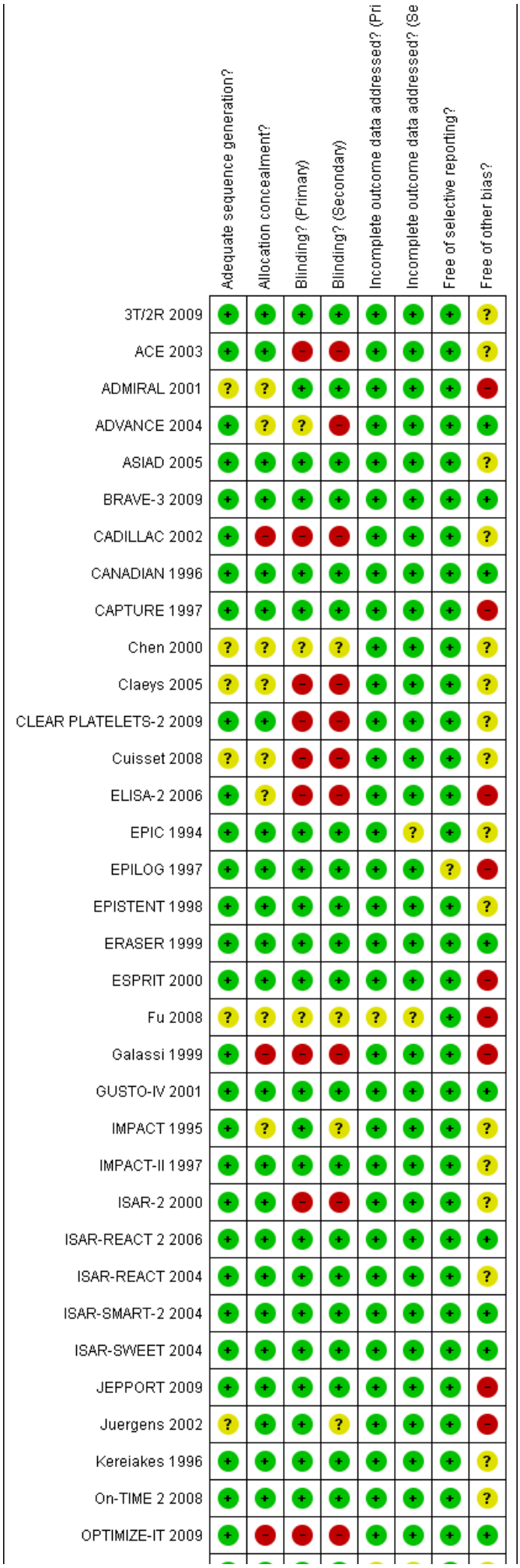
Figure 2

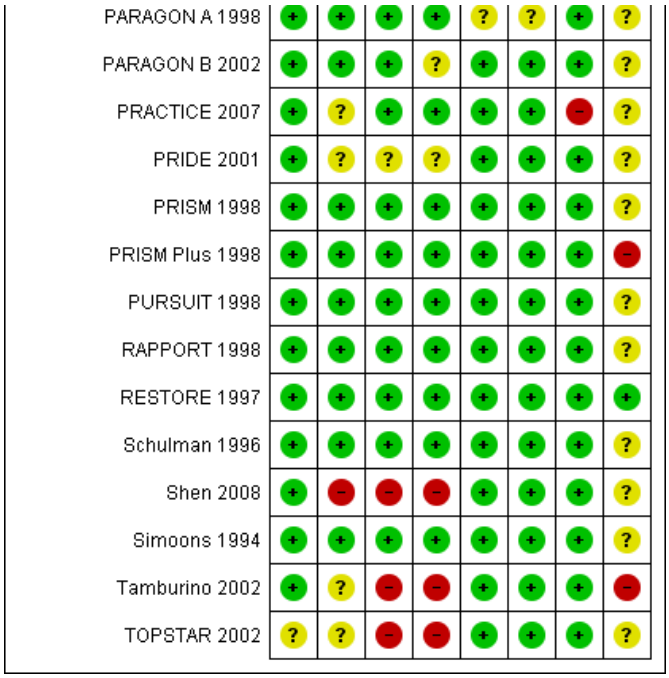


Caption

Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Figure 3

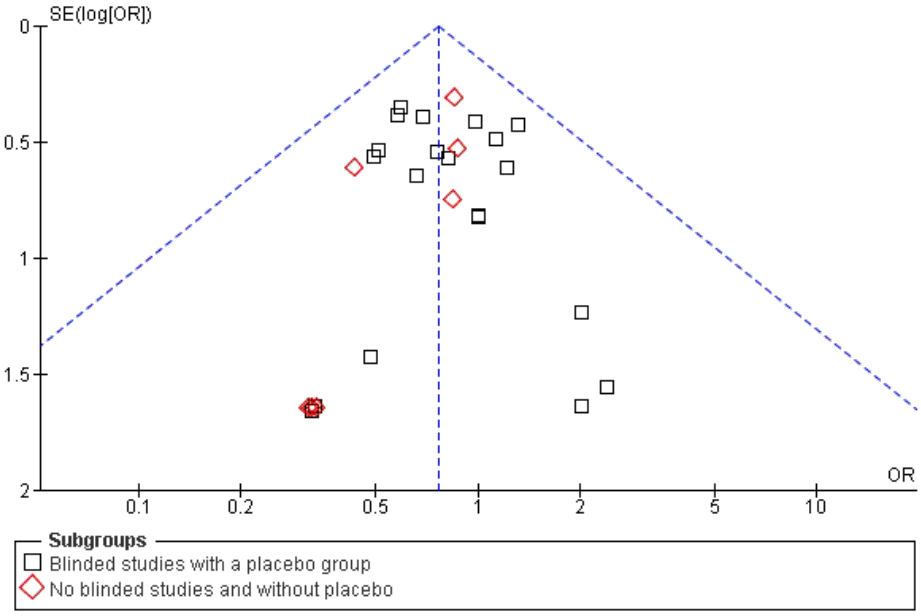

Adequate sequence generation?
Allocation concealment?
Blinding? (Primary)
Blinding? (Secondary)
Incomplete outcome data addressed? (Pri
Incomplete outcome data addressed? (Se
Free of selective reporting?
Free of other bias?
3T/2R 2009
ACE 2003
ADMIRAL 2001
ADVANCE 2004
ASIAD 2005
BRAVE-3 2009
CADILLAC 2002
CANADIAN 1996
CAPTURE 1997
Chen 2000
Claeys 2005
CLEAR PLATELETS-2 2009
Cuisset 2008
ELISA-2 2006
EPIC 1994
EPILOG 1997
EPISTENT 1998
ERASER 1999
ESPRIT 2000
Fu 2008
Galassi 1999
GUSTO-IV 2001
IMPACT 1995
IMPACT-II 1997
ISAR-2 2000
ISAR-REACT 2 2006
ISAR-REACT 2004
ISAR-SMART-2 2004
ISAR-SWEET 2004
JEPPORT 2009
Juergens 2002
Kereiakes 1996
On-TIME 2 2008
OPTIMIZE-IT 2009



Caption

Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

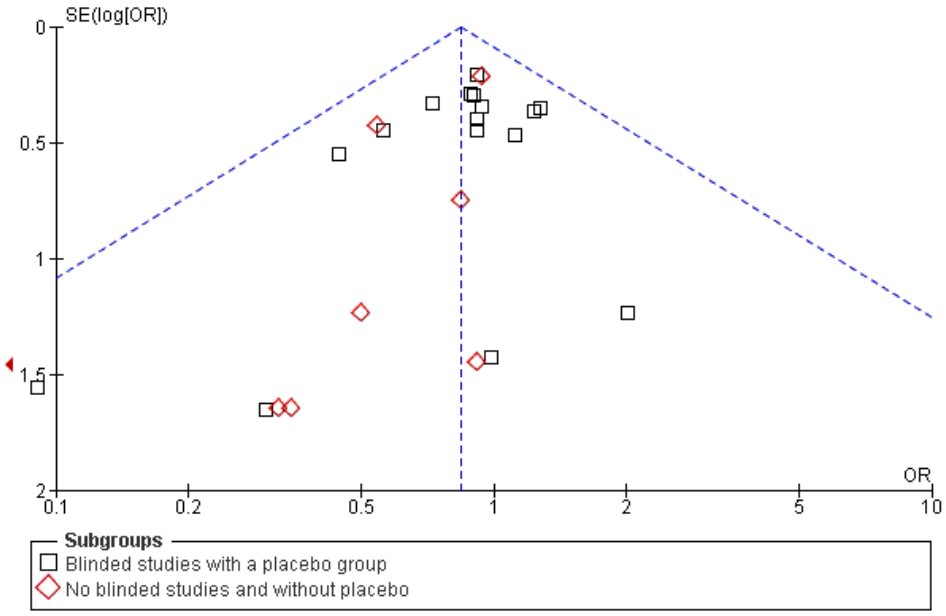
Figure 4 (Analysis 1.1)



Caption

Funnel plot of comparison: 1 During PCI (all patients), outcome: 1.1 30-day mortality.

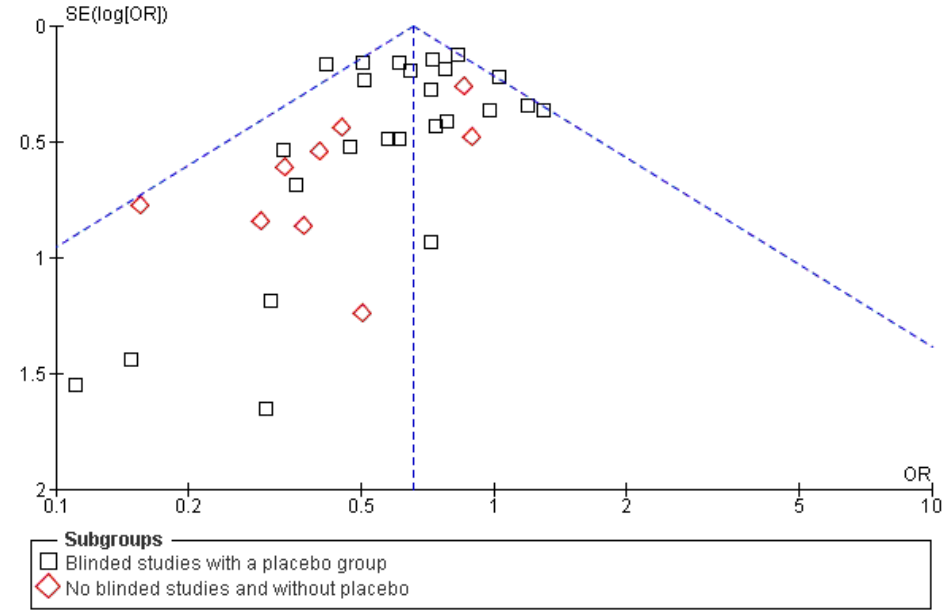
Figure 5 (Analysis 1.2)



Caption

Funnel plot of comparison: 1 During PCI (all patients), outcome: 1.2 6-month mortality.

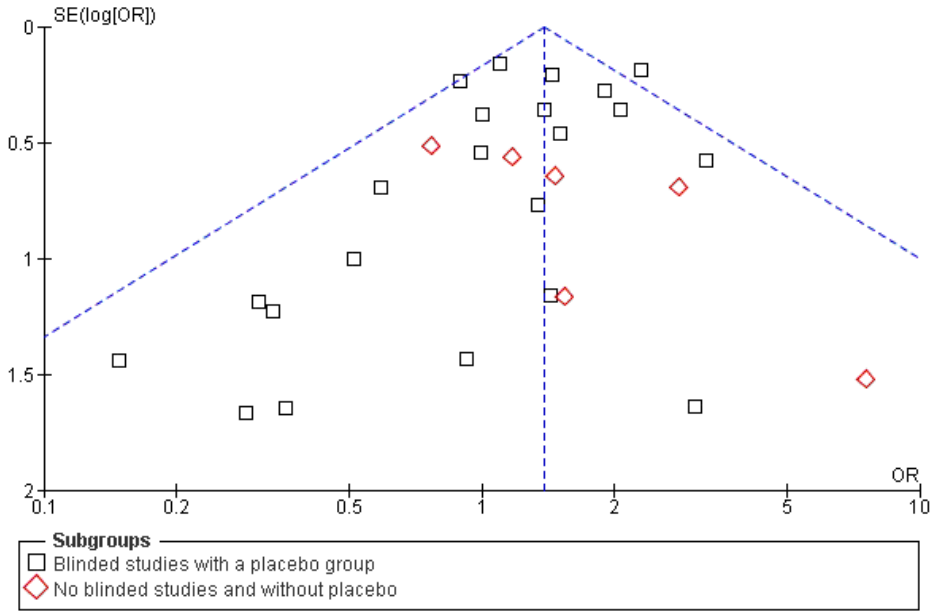
Figure 6 (Analysis 1.3)



Caption

Funnel plot of comparison: 1 During PCI (all patients), outcome: 1.3 30-day mortality or myocardial infarction.

Figure 7 (Analysis 1.9)



Caption

Funnel plot of comparison: 1 During PCI (all patients), outcome: 1.9 30-day major bleeding.

Sources of support

Internal sources

- University of Barcelona, Spain
- Institut Municipal d'Investigacio Medica, Barcelona, Spain

External sources

- FIS PI050120, Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, Spain
- Red HERACLES RD06/0009, Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, Spain
- EUPHORIC Project (Ref. 2003/134), Not specified
- FIS PI07/0640, Spain
  Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III

Feedback

Appendices

1 Search strategies for 2010 update

CENTRAL

#1 MeSH descriptor Platelet Glycoprotein GPIIb-IIIa Complex explode all trees
#2 (glycoprotein in All Text near/6 inhibit* in All Text)
#3 (glycoprotein in All Text near/6 block* in All Text)
#4 (glycoprotein in All Text near/6 antagonist* in All Text)
#5 gpiib* in All Text
#6 abciximab in All Text
#7 sibrafiban in All Text
#8 tirofiban in All Text
#9 lamifiban in All Text
#10 aggrastat in All Text
#11 eptifibatide in All Text
#12 xemilofiban in All Text
#13 lotrafiban in All Text
#14 orbofiban in All Text
#15 fradafiban in All Text 1
#16 fibrinogen next receptor next antagonist* in All Text
#17 roxifiban in All Text
#18 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
#19 (#11 or #12 or #13 or #14 or #15 or #16 or #17)
#20 (#18 or #19)
#21 MeSH descriptor Angioplasty, Transluminal, Percutaneous Coronary explode all trees
#22 ptca in All Text

#23 (coronary in All Text near/6 angioplasty in All Text)
#24 pci in All Text
#25 percutaneous next coronary next intervention* in All Text
#26 MeSH descriptor Angina, Unstable explode all trees
#27 angina in All Text
#28 stent* in All Text
#29 MeSH descriptor Myocardial Infarction explode all trees
#30 myocardial next infarction in All Text
#31 heart next infarction in All Text
#32 coronary next syndrome* in All Text
#33 non next st next segment in All Text
#34 non next st next elevation in All Text
#35 without next st next segment in All Text
#36 MeSH descriptor acute coronary syndrome this term only
#37 (#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
#38 (#31 or #32 or #33 or #34 or #35 or #36)
#39 (#37 or #38)
#40 (#20 and #39)

MEDLINE (on Ovid)

1 Platelet Glycoprotein GPIIb-IIIa Complex/
2 (glycoprotein adj5 (inhibit$ or block$ or antagonist$)).tw.
3 gpIIb$.tw.
4 abciximab.tw.
5 sibrafiban.tw.
6 tirofiban.tw.
7 lamifiban.tw.
8 aggrastat.tw.
9 eptifibatide.tw.
10 xemilofiban.tw.
11 lotrafiban.tw.
12 orbofiban.tw.
13 roxifiban.tw.
14 or/1-13
15 exp Angioplasty, Transluminal, Percutaneous Coronary/
16 ptca.tw.
17 (coronary adj5 angioplasty).tw.
18 exp Angina, Unstable/
19 angina.tw.
20 exp Stents/
21 stent$.tw.
22 exp Myocardial Infarction/
23 myocardial infarction.tw.
24 coronary syndrome$.tw.
25 Acute Coronary Syndrome/
26 pci.tw.
27 percutaneous coronary intervention$.tw.
28 or/15-27
29 14 and 28
30 randomized controlled trial.pt.
31 controlled clinical trial.pt.
32 Randomized controlled trials/
33 random allocation/
34 double blind method/
35 single-blind method/
36 or/30-35
37 exp animal/ not humans/
38 36 not 37
39 clinical trial.pt.
40 exp Clinical Trials as Topic/
41 (clin$ adj25 trial$).ti,ab.
42 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
43 placebos/
44 placebo$.ti,ab.
45 random$.ti,ab.
46 research design/
47 or/39-46

48 47 not 37
49 38 or 48
50 29 and 49
51 (2006$ or 2007$ or 2008$ or 2009$).em.
52 51 and 50

EMBASE (on Ovid)

1 exp Fibrinogen Receptor/
2 (glycoprotein adj5 (inhibit$ or block$ or antagonist$)).tw.
3 gpIIb$.tw.
4 abciximab.tw.
5 sibrafiban.tw.
6 tirofiban.tw.
7 lamifiban.tw.
8 aggrastat.tw.
9 eptifibatide.tw.
10 xemilofiban.tw.
11 lotrafiban.tw.
12 orbofiban.tw.
13 roxifiban.tw.
14 or/1-13
15 exp Transluminal Coronary Angioplasty/
16 ptca.tw.
17 (coronary adj5 angioplasty).tw.
18 exp Unstable Angina Pectoris/
19 angina.tw.
20 exp coronary stent/
21 stent$.tw.
22 exp Heart Infarction/
23 myocardial infarction.tw.
24 coronary syndrome$.tw.
25 pci.tw.
26 percutaneous coronary intervention$.tw.
27 acute coronary syndrome/
28 or/15-27
29 28 and 14
30 controlled clinical trial/
31 random$.tw.
32 randomized controlled trial/
33 follow-up.tw.
34 double blind procedure/
35 placebo$.tw.
36 placebo/
37 factorial$.ti,ab.
38 (crossover$ or cross-over$).ti,ab.
39 (double$ adj blind$).ti,ab.
40 (singl$ adj blind$).ti,ab.
41 assign$.ti,ab.
42 allocat$.ti,ab.
43 volunteer$.ti,ab.
44 Crossover Procedure/
45 Single Blind Procedure/
46 or/30-45
47 (exp animals/ or nonhuman/) not human/
48 46 not 47
49 29 and 48
50 (2006$ or 2007$ or 2008$ or 2009$).em.
51 50 and 49

2 Search strategies for 2007 update

Database: Ovid MEDLINE(R) <1966 to June 2006>

1 Platelet Glycoprotein GPIIb-IIIa Complex/
2 (glycoprotein adj5 (inhibit$ or block$ or antagonist$)).tw.
3 gpIIb$.tw.
4 abciximab.tw.
5 sibrafiban.tw.

6 tirofiban.tw.
7 lamifiban.tw.
8 aggrastat.tw.
9 eptifibatide.tw.
10 xemilofiban.tw.
11 lotrafiban.tw.
12 orbofiban.tw.
13 roxifiban.tw.
14 or/1-13
15 exp Angioplasty, Transluminal, Percutaneous Coronary/
16 ptca.tw.
17 (coronary adj5 angioplasty).tw.
18 exp Angina, Unstable/
19 angina.tw.
20 exp Stents/
21 stent$.tw.
22 exp Myocardial Infarction/
23 myocardial infarction.tw.
24 coronary syndrome$.tw.
25 pci.tw.
26 percutaneous coronary intervention$.tw.
27 or/15-26
28 14 and 27
29 randomized controlled trial.pt.
30 controlled clinical trial.pt.
31 Randomized controlled trials/
32 random allocation.sh.
33 double blind method.sh.
34 single-blind method.sh.
35 or/29-34
36 exp animal/ not human/
37 35 not 36
38 clinical trial.pt.
39 exp Clinical trials/
40 (clin$ adj25 trial$).ti,ab.
41 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
42 placebos.sh.
43 placebo$.ti,ab.
44 random$.ti,ab.
45 research design.sh.
46 or/38-45
47 46 not 36
48 37 or 47
49 28 and 48
50 limit 49 to yr=2001 - 2005

Database: EMBASE <1980 to 2006 Week 15>

1 exp Fibrinogen Receptor/
2 (glycoprotein adj5 (inhibit$ or block$ or antagonist$)).tw.
3 gpIIb$.tw.
4 abciximab.tw.
5 sibrafiban.tw.
6 tirofiban.tw.
7 lamifiban.tw.
8 aggrastat.tw.
9 eptifibatide.tw.
10 xemilofiban.tw.
11 lotrafiban.tw.
12 orbofiban.tw.
13 roxifiban.tw.
14 or/1-13
15 exp Transluminal Coronary Angioplasty/
16 ptca.tw.
17 (coronary adj5 angioplasty).tw.
18 exp Unstable Angina Pectoris/
19 angina.tw.
20 exp coronary stent/

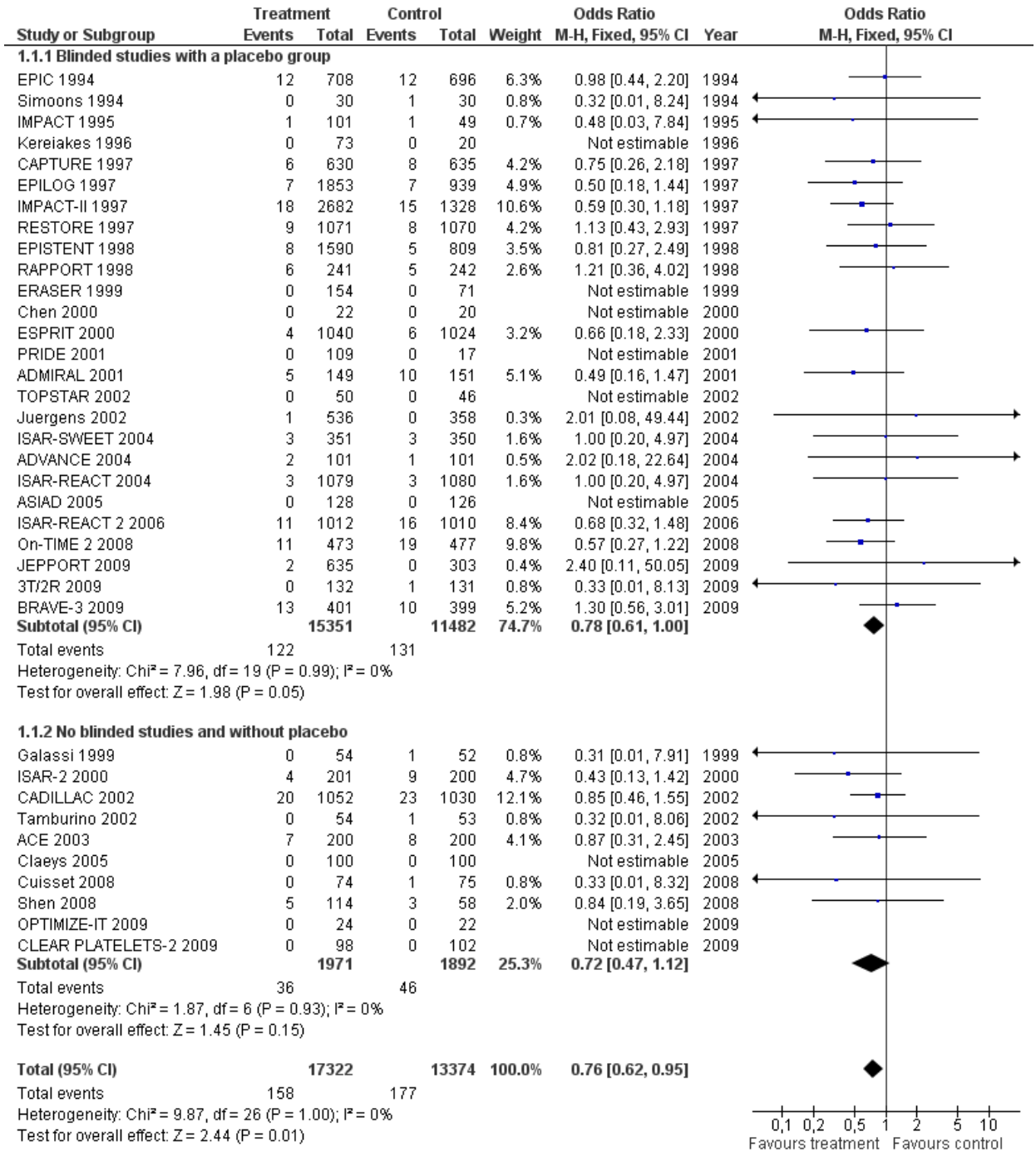
21 stent$.tw.
22 exp Heart Infarction/
23 myocardial infarction.tw.
24 coronary syndrome$.tw.
25 pci.tw.
26 percutaneous coronary intervention$.tw.
27 or/15-26
28 14 and 27
29 random$.ti,ab.
30 factorial$.ti,ab.
31 (crossover$ or cross over$ or cross-over$).ti,ab.
32 placebo$.ti,ab.
33 (double$ adj blind$).ti,ab.
34 (singl$ adj blind$).ti,ab.
35 assign$.ti,ab.
36 allocat$.ti,ab.
37 volunteer$.ti,ab.
38 Crossover Procedure/
39 Double Blind Procedure/
40 Randomized Controlled Trial/
41 Single Blind Procedure/
42 or/29-41
43 exp animal/
44 nonhuman/
45 exp animal experiment/
46 or/43-45
47 exp human/
48 46 not 47
49 42 not 48
50 49 and 28
51 limit 50 to yr=2000 - 2005
52 from 51 keep 1-569

3 MEDLINE search strategy for original review (2001)

1 Clinical trial/ or Phase 1 clinical trial/ or Phase 2 clinical trial/ or Phase 3 clinical trial/ or Phase 4 clinical trial/ or Randomized controlled trial/
2 Randomization/
3 Double blind procedure/ or Meta analysis/ or Single blind procedure/
4 exp controlled study/
5 Placebo/
6 ["150".tg.]
7 ["197".tg.]
8 (clinic$ adj10 trial).ti,ab.
9 (clinic$ adj10 trial$).ti,ab.
10 (controlled adj trial$).ti,ab.
11 ((singl$ or doubl$ or trebl$ or tripl$) adj10 (blind$ or mask$)).ti,ab.
12 (placebo$ or random$).ti,ab.
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 9 or 10 or 11 or 12
14limit 13 to human
15("glycoprotein IIb/IIIa" or "glycoprotein IIb-IIIa" or "glycoprotein-IIb/IIIa" or "Platelet IIb/IIIa" or "GP IIb-IIIa" or "GP IIb/IIIa" or "IIb" or "IIIa").mp. [mp=Title, Abstract, registry number word, mesh subject heading]
16(Abciximab or 7E3 or Sibrafiban or Tirofiban or MK-383 or lamifiban or Aggrastat or Eptifibatide or Xemilofiban or Sibrafiban or Orbofiban or Lefradafiban or Integrilin or Integrelin or Fradafiban or Lefradafiban).mp. [mp=Title, Abstract, registry number word, mesh subject heading]
17(Inhibitor$ or block$ or antagonist$).mp. [mp=Title, Abstract, registry number word, mesh subject heading]
1814 and (15 or 16) and 17

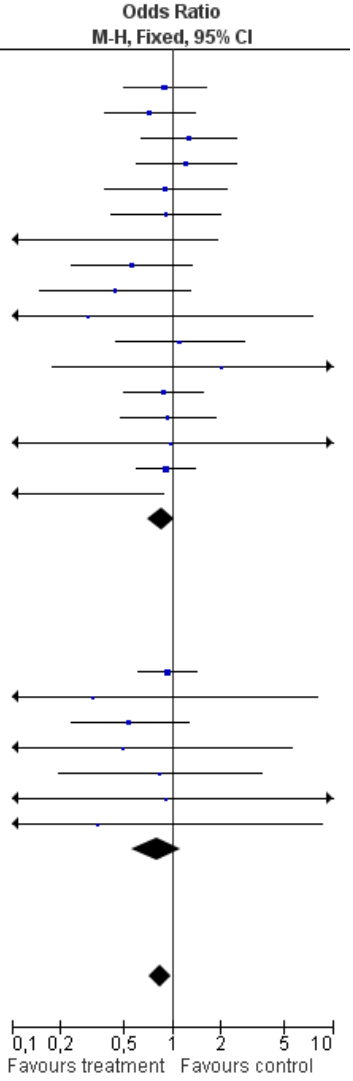
Graphs

1.1 30-day mortality

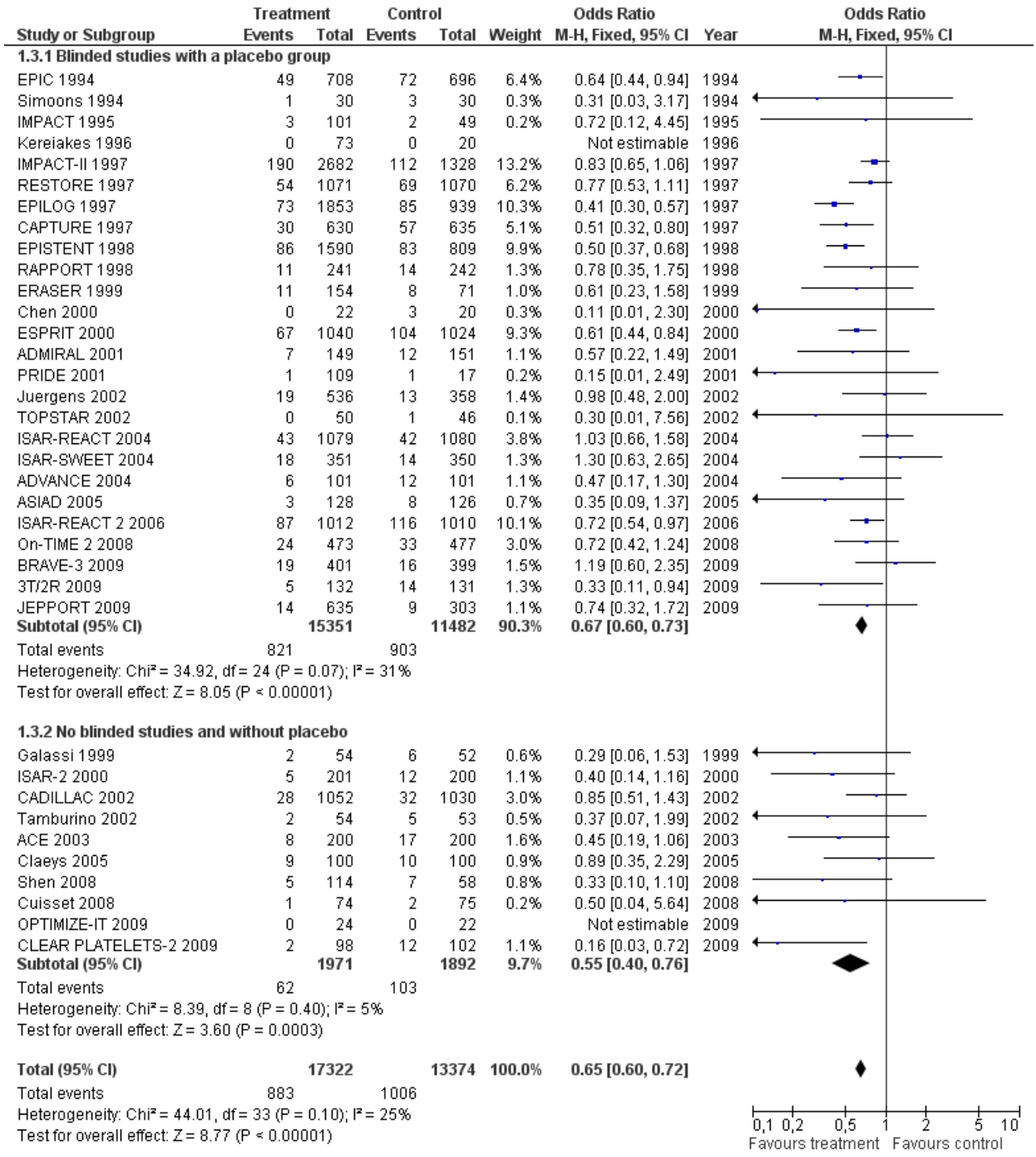


1.2 6-month mortality

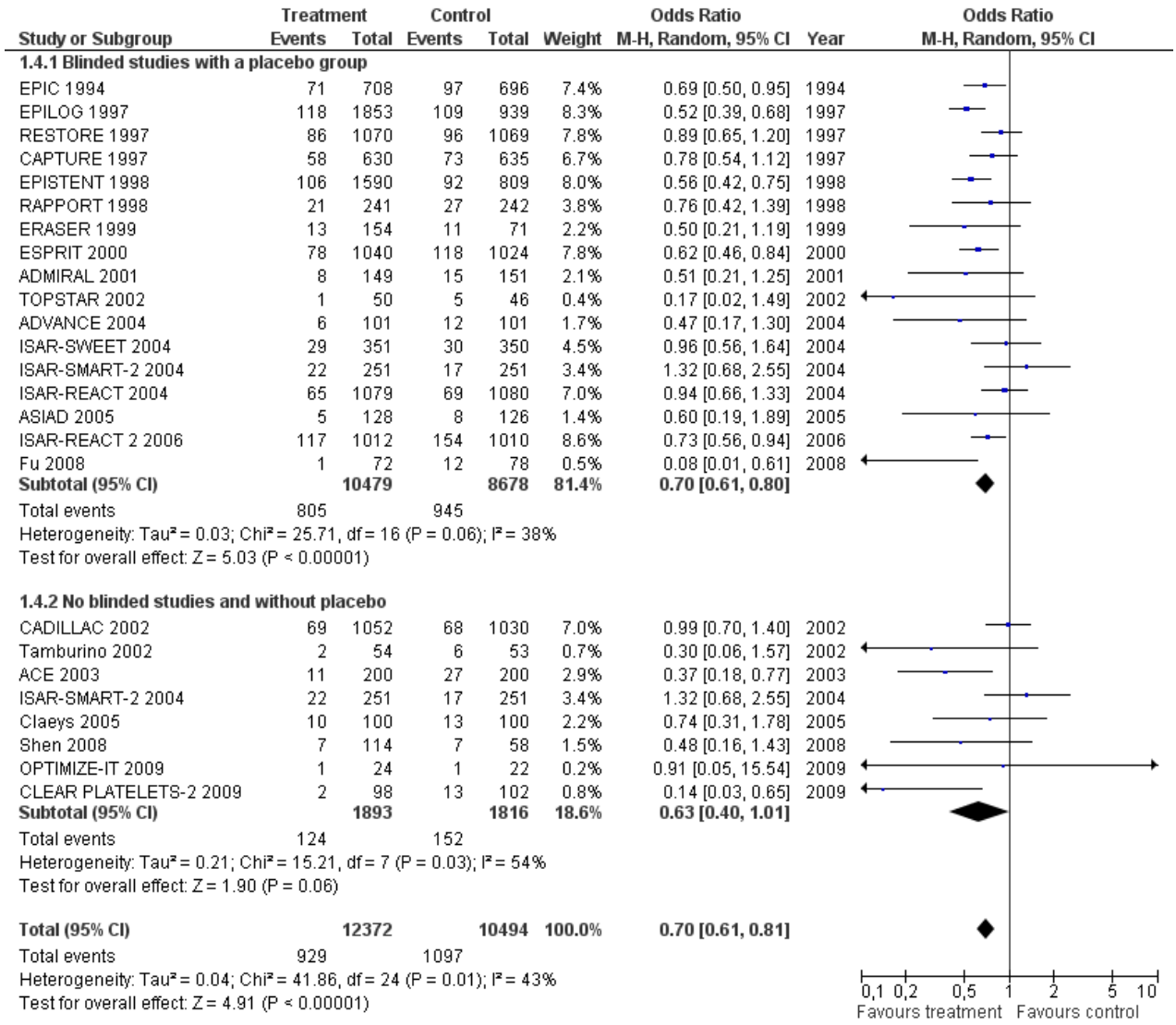
Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
1.2.1 Blinded studies with a placebo group							
EPIC 1994	22	708	24	696	7.7%	0.90 [0.50, 1.62]	1994
EPILOG 1997	23	1853	16	939	6.9%	0.73 [0.38, 1.38]	1997
RESTORE 1997	19	1070	15	1069	4.9%	1.27 [0.64, 2.51]	1997
CAPTURE 1997	17	630	14	635	4.5%	1.23 [0.60, 2.52]	1997
RAPPORT 1998	10	241	11	242	3.5%	0.91 [0.38, 2.18]	1998
EPISTENT 1998	18	1590	10	809	4.3%	0.91 [0.42, 1.99]	1998
ERASER 1999	0	154	2	71	1.1%	0.09 [0.00, 1.90]	1999
ESPRIT 2000	8	1040	14	1024	4.6%	0.56 [0.23, 1.34]	2000
ADMIRAL 2001	5	149	11	151	3.5%	0.44 [0.15, 1.30]	2001
TOPSTAR 2002	0	50	1	46	0.5%	0.30 [0.01, 7.56]	2002
ISAR-SMART-2 2004	10	251	9	251	2.8%	1.12 [0.45, 2.79]	2004
ADVANCE 2004	2	101	1	101	0.3%	2.02 [0.18, 22.64]	2004
ISAR-REACT 2004	23	1079	26	1080	8.4%	0.88 [0.50, 1.56]	2004
ISAR-SWEET 2004	17	351	18	350	5.6%	0.94 [0.48, 1.85]	2004
ASIAD 2005	1	128	1	126	0.3%	0.98 [0.06, 15.91]	2005
ISAR-REACT 2 2006	45	1012	49	1010	15.4%	0.91 [0.60, 1.38]	2006
Fu 2008	0	72	9	78	3.0%	0.05 [0.00, 0.88]	2008
Subtotal (95% CI)		**10479**		**8678**	**77.4%**	**0.85 [0.71, 1.03]**	
Total events	220		231				
Heterogeneity: Chi² = 12.20, df = 16 (P = 0.73); I² = 0%							
Test for overall effect: Z = 1.64 (P = 0.10)							
1.2.2 No blinded studies and without placebo							
CADILLAC 2002	43	1052	45	1030	14.4%	0.93 [0.61, 1.43]	2002
Tamburino 2002	0	54	1	53	0.5%	0.32 [0.01, 8.06]	2002
ACE 2003	9	200	16	200	5.0%	0.54 [0.23, 1.26]	2003
Claeys 2005	1	100	2	100	0.7%	0.49 [0.04, 5.55]	2005
Shen 2008	5	114	3	58	1.3%	0.84 [0.19, 3.65]	2008
OPTIMIZE-IT 2009	1	24	1	22	0.3%	0.91 [0.05, 15.54]	2009
CLEAR PLATELETS-2 2009	0	98	1	102	0.5%	0.34 [0.01, 8.53]	2009
Subtotal (95% CI)		**1642**		**1565**	**22.6%**	**0.80 [0.56, 1.14]**	
Total events	59		69				
Heterogeneity: Chi² = 2.06, df = 6 (P = 0.91); I² = 0%							
Test for overall effect: Z = 1.22 (P = 0.22)							
Total (95% CI)		**12121**		**10243**	**100.0%**	**0.84 [0.71, 1.00]**	
Total events	279		300				
Heterogeneity: Chi² = 14.42, df = 23 (P = 0.91); I² = 0%							
Test for overall effect: Z = 2.02 (P = 0.04)							



1.3 30-day mortality or myocardial infarction



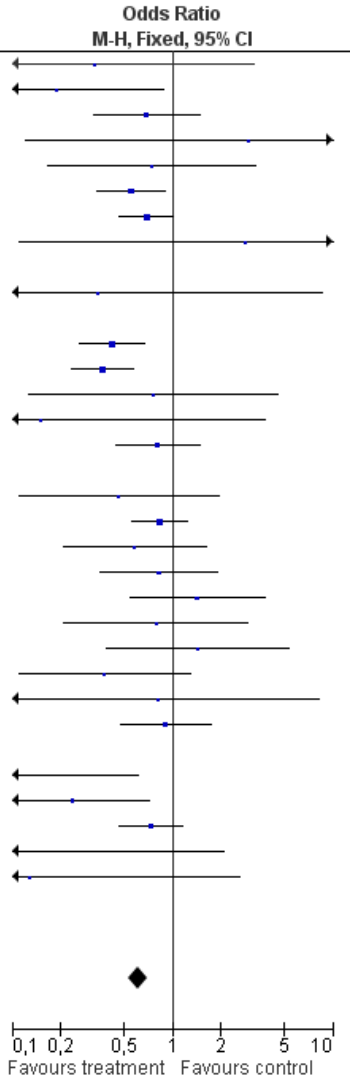
1.4 6-month mortality or myocardial infarction



1.5 30-day urgent revascularisation

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ACE 2003	1	200	3	200	0.6%	0.33 [0.03, 3.20]
ADMIRAL 2001	2	149	10	151	2.0%	0.19 [0.04, 0.89]
ADVANCE 2004	14	101	19	101	3.4%	0.69 [0.33, 1.48]
ASIAD 2005	1	128	0	126	0.1%	2.98 [0.12, 73.76]
BRAVE-3 2009	3	401	4	399	0.8%	0.74 [0.17, 3.35]
CADILLAC 2002	26	1052	45	1030	9.2%	0.55 [0.34, 0.91]
CAPTURE 1997	49	630	69	635	13.1%	0.69 [0.47, 1.02]
Chen 2000	1	22	0	20	0.1%	2.86 [0.11, 74.31]
Claeys 2005	0	100	0	100		Not estimable
CLEAR PLATELETS-2 2009	0	98	1	102	0.3%	0.34 [0.01, 8.53]
Cuisset 2008	0	74	0	75		Not estimable
EPIC 1994	27	708	60	696	12.0%	0.42 [0.26, 0.67]
EPILOG 1997	36	1853	48	939	12.9%	0.37 [0.24, 0.57]
EPISTENT 1998	3	1590	2	809	0.5%	0.76 [0.13, 4.57]
ERASER 1999	0	154	1	71	0.4%	0.15 [0.01, 3.78]
ESPRIT 2000	20	1040	24	1024	4.9%	0.82 [0.45, 1.49]
Galassi 1999	0	54	0	52		Not estimable
IMPACT 1995	4	101	4	49	1.1%	0.46 [0.11, 1.94]
IMPACT-II 1997	66	2682	39	1328	10.5%	0.83 [0.56, 1.25]
ISAR-2 2000	6	201	10	200	2.0%	0.58 [0.21, 1.64]
ISAR-REACT 2 2006	10	1012	12	1010	2.5%	0.83 [0.36, 1.93]
ISAR-REACT 2004	10	1079	7	1080	1.4%	1.43 [0.54, 3.78]
ISAR-SWEET 2004	4	351	5	350	1.0%	0.80 [0.21, 2.99]
JEPPORT 2009	9	635	3	303	0.8%	1.44 [0.39, 5.35]
Juergens 2002	4	536	7	358	1.7%	0.38 [0.11, 1.30]
Kereiakes 1996	3	73	1	20	0.3%	0.81 [0.08, 8.28]
On-TIME 2 2008	18	473	20	477	4.0%	0.90 [0.47, 1.73]
OPTIMIZE-IT 2009	0	24	0	22		Not estimable
PRIDE 2001	0	109	2	17	0.9%	0.03 [0.00, 0.62]
RAPPORT 1998	4	241	16	242	3.2%	0.24 [0.08, 0.72]
RESTORE 1997	32	1071	43	1070	8.6%	0.74 [0.46, 1.17]
Shen 2008	0	114	2	58	0.7%	0.10 [0.00, 2.09]
Simoons 1994	0	30	3	30	0.7%	0.13 [0.01, 2.61]
Tamburino 2002	0	54	0	53		Not estimable
TOPSTAR 2002	0	50	0	46		Not estimable
Total (95% CI)		**17190**		**13243**	**100.0%**	**0.61 [0.53, 0.70]**
Total events	353		460			

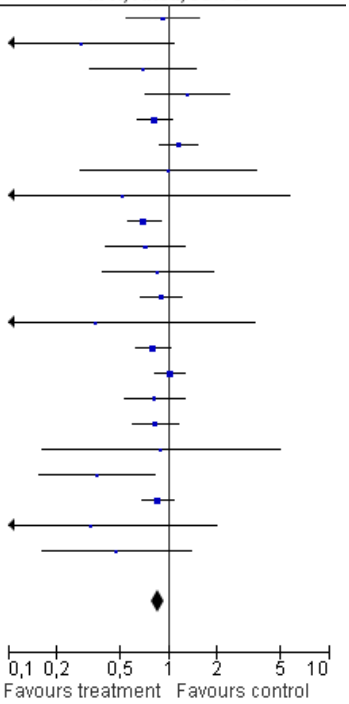
Heterogeneity: Chi² = 33.73, df = 28 (P = 0.21); I² = 17%
Test for overall effect: Z = 6.77 (P < 0.00001)



1.6 6-month urgent revascularisation

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ACE 2003	32	200	34	200	2.3%	0.93 [0.55, 1.58]
ADMIRAL 2001	3	149	10	151	0.8%	0.29 [0.08, 1.07]
ADVANCE 2004	14	101	19	101	1.3%	0.69 [0.33, 1.48]
ASIAD 2005	29	128	23	126	1.5%	1.31 [0.71, 2.42]
CADILLAC 2002	128	1052	148	1030	10.8%	0.83 [0.64, 1.06]
CAPTURE 1997	135	630	120	635	7.7%	1.17 [0.89, 1.54]
Claeys 2005	5	100	5	100	0.4%	1.00 [0.28, 3.57]
CLEAR PLATELETS-2 2009	1	98	2	102	0.2%	0.52 [0.05, 5.78]
EPIC 1994	161	708	205	696	13.1%	0.70 [0.55, 0.90]
EPISTENT 1998	30	1590	21	809	2.2%	0.72 [0.41, 1.27]
ERASER 1999	21	154	11	71	1.1%	0.86 [0.39, 1.90]
ESPRIT 2000	89	1040	96	1024	7.3%	0.90 [0.67, 1.22]
Fu 2008	1	72	3	78	0.2%	0.35 [0.04, 3.46]
ISAR-REACT 2 2006	137	1012	164	1010	11.6%	0.81 [0.63, 1.03]
ISAR-REACT 2004	208	1079	204	1080	13.5%	1.03 [0.83, 1.27]
ISAR-SMART-2 2004	47	251	55	251	3.7%	0.82 [0.53, 1.27]
ISAR-SWEET 2004	84	351	96	350	6.0%	0.83 [0.59, 1.17]
OPTIMIZE-IT 2009	3	24	3	22	0.2%	0.90 [0.16, 5.03]
RAPPORT 1998	8	241	21	242	1.7%	0.36 [0.16, 0.83]
RESTORE 1997	172	1070	194	1069	13.4%	0.86 [0.69, 1.08]
Shen 2008	2	114	3	58	0.3%	0.33 [0.05, 2.02]
Tamburino 2002	6	54	11	53	0.8%	0.48 [0.16, 1.40]
Total (95% CI)		**10218**		**9258**	**100.0%**	**0.86 [0.79, 0.94]**
Total events	1316		1448			

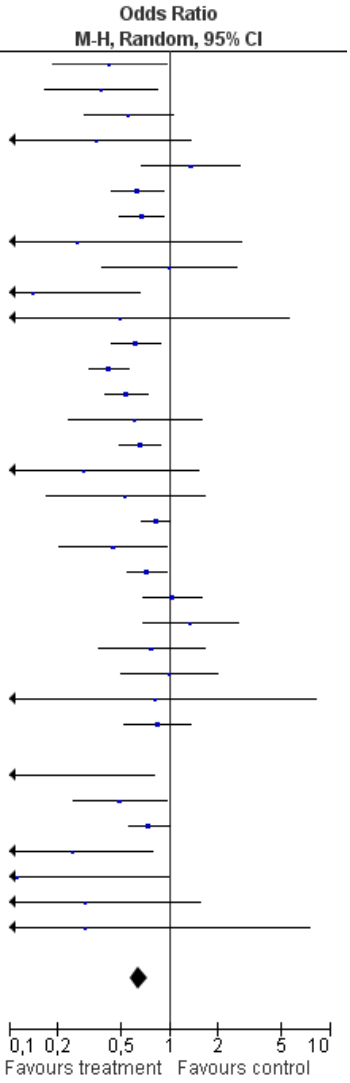
Heterogeneity: Chi² = 23.01, df = 21 (P = 0.34); I² = 9%
Test for overall effect: Z = 3.56 (P = 0.0004)



1.7 30-day mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ACE 2003	9	200	20	200	2.0%	0.42 [0.19, 0.96]
ADMIRAL 2001	9	149	22	151	2.0%	0.38 [0.17, 0.85]
ADVANCE 2004	20	101	31	101	2.9%	0.56 [0.29, 1.06]
ASIAD 2005	3	128	8	126	0.8%	0.35 [0.09, 1.37]
BRAVE-3 2009	19	401	14	399	2.5%	1.37 [0.68, 2.77]
CADILLAC 2002	48	1052	72	1030	5.5%	0.64 [0.44, 0.93]
CAPTURE 1997	71	630	101	635	6.2%	0.67 [0.48, 0.93]
Chen 2000	1	22	3	20	0.3%	0.27 [0.03, 2.83]
Claeys 2005	9	100	9	100	1.5%	1.00 [0.38, 2.63]
CLEAR PLATELETS-2 2009	2	98	13	102	0.7%	0.14 [0.03, 0.65]
Cuisset 2008	1	74	2	75	0.3%	0.50 [0.04, 5.64]
EPIC 1994	59	708	89	696	5.9%	0.62 [0.44, 0.88]
EPILOG 1997	97	1853	109	939	6.9%	0.42 [0.32, 0.56]
EPISTENT 1998	97	1590	87	809	6.6%	0.54 [0.40, 0.73]
ERASER 1999	11	154	8	71	1.6%	0.61 [0.23, 1.58]
ESPRIT 2000	78	1040	113	1024	6.6%	0.65 [0.48, 0.88]
Galassi 1999	2	54	6	52	0.6%	0.29 [0.06, 1.53]
IMPACT 1995	7	101	6	49	1.1%	0.53 [0.17, 1.68]
IMPACT-II 1997	256	2682	151	1328	8.1%	0.82 [0.66, 1.02]
ISAR-2 2000	10	201	21	200	2.2%	0.45 [0.20, 0.97]
ISAR-REACT 2 2006	90	1012	120	1010	6.8%	0.72 [0.54, 0.97]
ISAR-REACT 2004	45	1079	43	1080	4.9%	1.05 [0.68, 1.61]
ISAR-SWEET 2004	20	351	15	350	2.6%	1.35 [0.68, 2.68]
JEPPORT 2009	18	635	11	303	2.3%	0.77 [0.36, 1.66]
Juergens 2002	21	536	14	358	2.6%	1.00 [0.50, 2.00]
Kereiakes 1996	3	73	1	20	0.3%	0.81 [0.08, 8.28]
On-TIME 2 2008	33	473	39	477	4.2%	0.84 [0.52, 1.36]
OPTIMIZE-IT 2009	0	24	0	22		Not estimable
PRIDE 2001	1	109	2	17	0.3%	0.07 [0.01, 0.81]
RAPPORT 1998	14	241	27	242	2.7%	0.49 [0.25, 0.96]
RESTORE 1997	86	1071	112	1070	6.7%	0.75 [0.56, 1.00]
Shen 2008	5	114	9	58	1.1%	0.25 [0.08, 0.78]
Simoons 1994	1	30	7	30	0.3%	0.11 [0.01, 0.99]
Tamburino 2002	2	54	6	53	0.6%	0.30 [0.06, 1.57]
TOPSTAR 2002	0	50	1	46	0.2%	0.30 [0.01, 7.56]
Total (95% CI)		**17190**		**13243**	**100.0%**	**0.64 [0.57, 0.73]**
Total events	1148		1292			

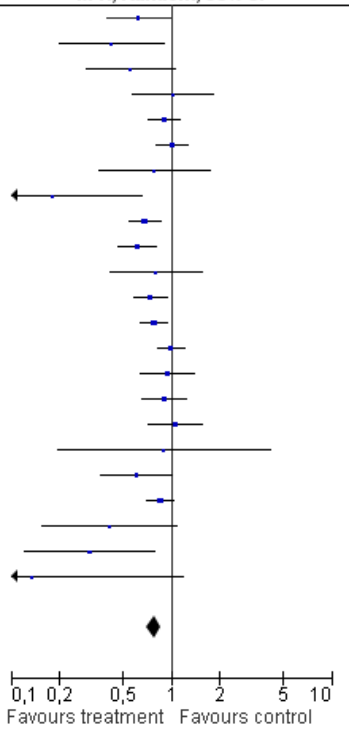
Heterogeneity: Tau² = 0.04; Chi² = 53.73, df = 33 (P = 0.01); I² = 39%
Test for overall effect: Z = 6.65 (P < 0.00001)



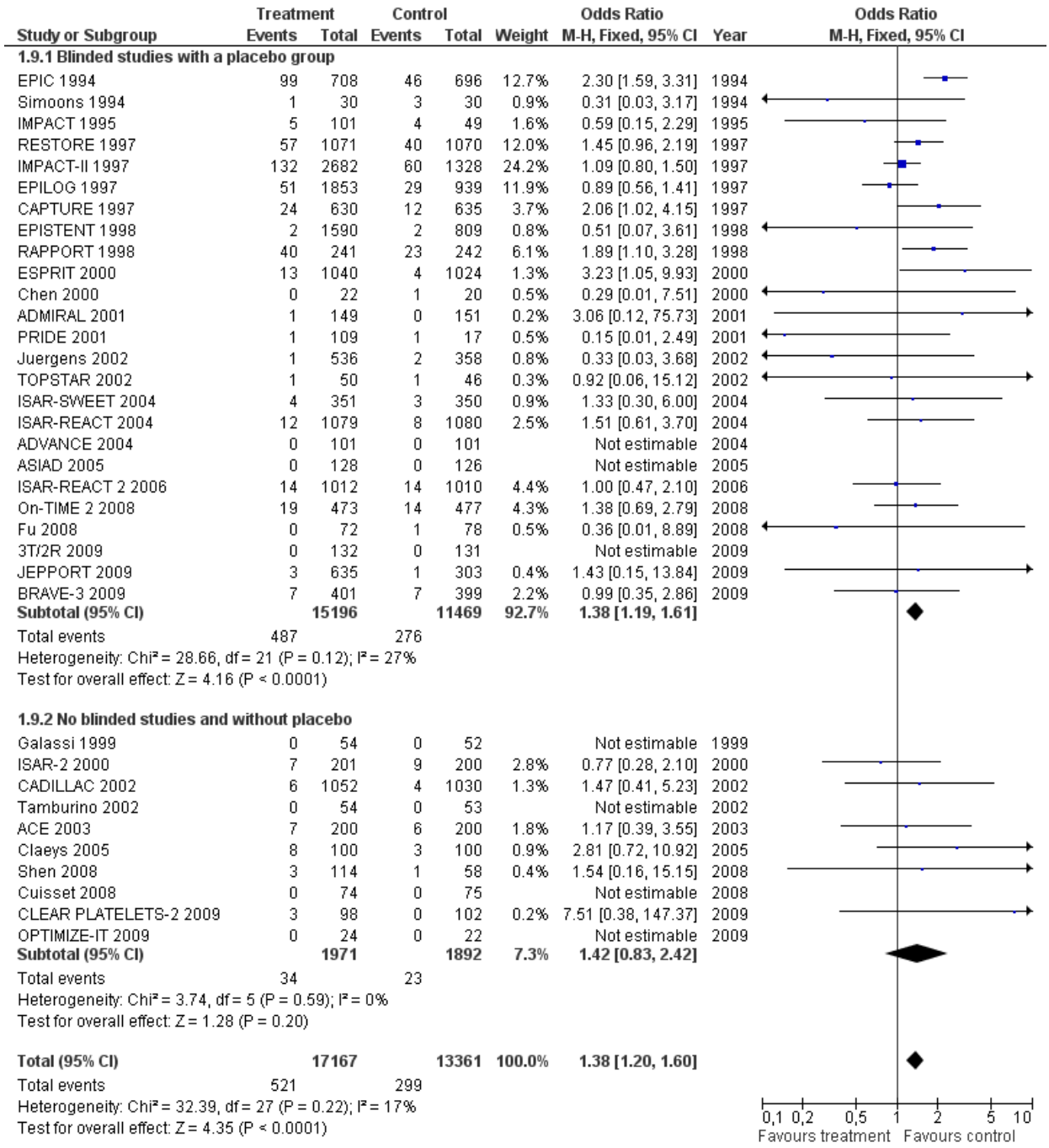
1.8 6-month mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ACE 2003	43	200	61	200	3.8%	0.62 [0.40, 0.98]
ADMIRAL 2001	11	149	24	151	1.7%	0.42 [0.20, 0.90]
ADVANCE 2004	20	101	31	101	2.2%	0.56 [0.29, 1.06]
ASIAD 2005	29	128	28	126	2.6%	1.03 [0.57, 1.85]
CADILLAC 2002	178	1052	190	1030	8.0%	0.90 [0.72, 1.13]
CAPTURE 1997	193	630	193	635	7.6%	1.01 [0.80, 1.28]
Claeys 2005	13	100	16	100	1.6%	0.78 [0.36, 1.73]
CLEAR PLATELETS-2 2009	3	98	15	102	0.7%	0.18 [0.05, 0.65]
EPIC 1994	191	708	244	696	7.9%	0.68 [0.55, 0.86]
EPISTENT 1998	124	1590	98	809	6.7%	0.61 [0.46, 0.81]
ERASER 1999	33	154	18	71	2.1%	0.80 [0.42, 1.55]
ESPRIT 2000	148	1040	187	1024	7.7%	0.74 [0.59, 0.94]
ISAR-REACT 2 2006	234	1012	281	1010	8.6%	0.78 [0.64, 0.95]
ISAR-REACT 2004	257	1079	257	1080	8.7%	1.00 [0.82, 1.22]
ISAR-SMART-2 2004	69	251	72	251	4.7%	0.94 [0.64, 1.39]
ISAR-SWEET 2004	105	351	112	350	5.8%	0.91 [0.66, 1.25]
JEPPORT 2009	95	635	43	303	4.7%	1.06 [0.72, 1.57]
OPTIMIZE-IT 2009	4	24	4	22	0.5%	0.90 [0.20, 4.14]
RAPPORT 1998	28	241	43	242	3.2%	0.61 [0.36, 1.02]
RESTORE 1997	258	1070	290	1069	8.8%	0.85 [0.70, 1.04]
Shen 2008	9	114	10	58	1.1%	0.41 [0.16, 1.08]
Tamburino 2002	8	54	19	53	1.2%	0.31 [0.12, 0.79]
TOPSTAR 2002	1	50	6	46	0.2%	0.14 [0.02, 1.18]
Total (95% CI)		**10831**		**9529**	**100.0%**	**0.78 [0.71, 0.87]**
Total events	2054		2242			

Heterogeneity: Tau² = 0.02; Chi² = 39.36, df = 22 (P = 0.01); I² = 44%
Test for overall effect: Z = 4.49 (P < 0.00001)

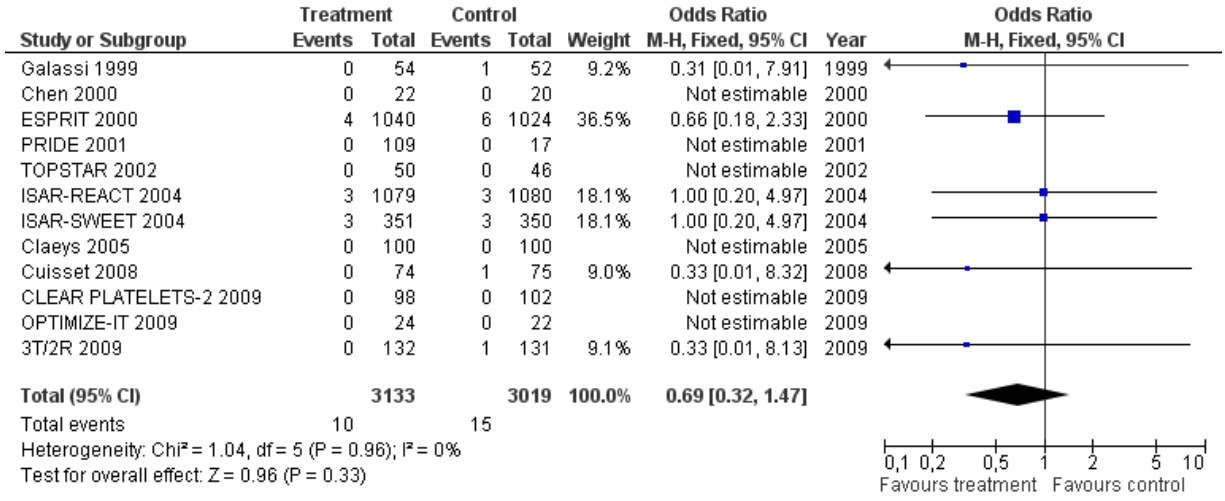


1.9 30-day major bleeding



Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
1.9.1 Blinded studies with a placebo group							
EPIC 1994	99	708	46	696	12.7%	2.30 [1.59, 3.31]	1994
Simoons 1994	1	30	3	30	0.9%	0.31 [0.03, 3.17]	1994
IMPACT 1995	5	101	4	49	1.6%	0.59 [0.15, 2.29]	1995
RESTORE 1997	57	1071	40	1070	12.0%	1.45 [0.96, 2.19]	1997
IMPACT-II 1997	132	2682	60	1328	24.2%	1.09 [0.80, 1.50]	1997
EPILOG 1997	51	1853	29	939	11.9%	0.89 [0.56, 1.41]	1997
CAPTURE 1997	24	630	12	635	3.7%	2.06 [1.02, 4.15]	1997
EPISTENT 1998	2	1590	2	809	0.8%	0.51 [0.07, 3.61]	1998
RAPPORT 1998	40	241	23	242	6.1%	1.89 [1.10, 3.28]	1998
ESPRIT 2000	13	1040	4	1024	1.3%	3.23 [1.05, 9.93]	2000
Chen 2000	0	22	1	20	0.5%	0.29 [0.01, 7.51]	2000
ADMIRAL 2001	1	149	0	151	0.2%	3.06 [0.12, 75.73]	2001
PRIDE 2001	1	109	1	17	0.5%	0.15 [0.01, 2.49]	2001
Juergens 2002	1	536	2	358	0.8%	0.33 [0.03, 3.68]	2002
TOPSTAR 2002	1	50	1	46	0.3%	0.92 [0.06, 15.12]	2002
ISAR-SWEET 2004	4	351	3	350	0.9%	1.33 [0.30, 6.00]	2004
ISAR-REACT 2004	12	1079	8	1080	2.5%	1.51 [0.61, 3.70]	2004
ADVANCE 2004	0	101	0	101		Not estimable	2004
ASIAD 2005	0	128	0	126		Not estimable	2005
ISAR-REACT 2 2006	14	1012	14	1010	4.4%	1.00 [0.47, 2.10]	2006
On-TIME 2 2008	19	473	14	477	4.3%	1.38 [0.69, 2.79]	2008
Fu 2008	0	72	1	78	0.5%	0.36 [0.01, 8.89]	2008
3T/2R 2009	0	132	0	131		Not estimable	2009
JEPPORT 2009	3	635	1	303	0.4%	1.43 [0.15, 13.84]	2009
BRAVE-3 2009	7	401	7	399	2.2%	0.99 [0.35, 2.86]	2009
Subtotal (95% CI)		**15196**		**11469**	**92.7%**	**1.38 [1.19, 1.61]**	
Total events	487		276				
Heterogeneity: Chi² = 28.66, df = 21 (P = 0.12); I² = 27%							
Test for overall effect: Z = 4.16 (P < 0.0001)							
1.9.2 No blinded studies and without placebo							
Galassi 1999	0	54	0	52		Not estimable	1999
ISAR-2 2000	7	201	9	200	2.8%	0.77 [0.28, 2.10]	2000
CADILLAC 2002	6	1052	4	1030	1.3%	1.47 [0.41, 5.23]	2002
Tamburino 2002	0	54	0	53		Not estimable	2002
ACE 2003	7	200	6	200	1.8%	1.17 [0.39, 3.55]	2003
Claeys 2005	8	100	3	100	0.9%	2.81 [0.72, 10.92]	2005
Shen 2008	3	114	1	58	0.4%	1.54 [0.16, 15.15]	2008
Cuisset 2008	0	74	0	75		Not estimable	2008
CLEAR PLATELETS-2 2009	3	98	0	102	0.2%	7.51 [0.38, 147.37]	2009
OPTIMIZE-IT 2009	0	24	0	22		Not estimable	2009
Subtotal (95% CI)		**1971**		**1892**	**7.3%**	**1.42 [0.83, 2.42]**	
Total events	34		23				
Heterogeneity: Chi² = 3.74, df = 5 (P = 0.59); I² = 0%							
Test for overall effect: Z = 1.28 (P = 0.20)							
Total (95% CI)		**17167**		**13361**	**100.0%**	**1.38 [1.20, 1.60]**	
Total events	521		299				
Heterogeneity: Chi² = 32.39, df = 27 (P = 0.22); I² = 17%							
Test for overall effect: Z = 4.35 (P < 0.0001)							

2.1 30-day mortality

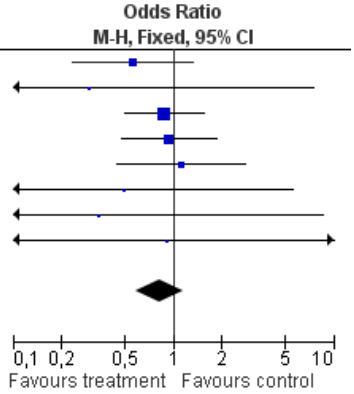


Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Galassi 1999	0	54	1	52	9.2%	0.31 [0.01, 7.91]	1999
Chen 2000	0	22	0	20		Not estimable	2000
ESPRIT 2000	4	1040	6	1024	36.5%	0.66 [0.18, 2.33]	2000
PRIDE 2001	0	109	0	17		Not estimable	2001
TOPSTAR 2002	0	50	0	46		Not estimable	2002
ISAR-REACT 2004	3	1079	3	1080	18.1%	1.00 [0.20, 4.97]	2004
ISAR-SWEET 2004	3	351	3	350	18.1%	1.00 [0.20, 4.97]	2004
Claeys 2005	0	100	0	100		Not estimable	2005
Cuisset 2008	0	74	1	75	9.0%	0.33 [0.01, 8.32]	2008
CLEAR PLATELETS-2 2009	0	98	0	102		Not estimable	2009
OPTIMIZE-IT 2009	0	24	0	22		Not estimable	2009
3T/2R 2009	0	132	1	131	9.1%	0.33 [0.01, 8.13]	2009
Total (95% CI)		**3133**		**3019**	**100.0%**	**0.69 [0.32, 1.47]**	
Total events	10		15				
Heterogeneity: Chi² = 1.04, df = 5 (P = 0.96); I² = 0%							
Test for overall effect: Z = 0.96 (P = 0.33)							

2.2 6-month mortality

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
ESPRIT 2000	8	1040	14	1024	19.7%	0.56 [0.23, 1.34]	2000
TOPSTAR 2002	0	50	1	46	2.2%	0.30 [0.01, 7.56]	2002
ISAR-REACT 2004	23	1079	26	1080	35.7%	0.88 [0.50, 1.56]	2004
ISAR-SWEET 2004	17	351	18	350	24.1%	0.94 [0.48, 1.85]	2004
ISAR-SMART-2 2004	10	251	9	251	12.1%	1.12 [0.45, 2.79]	2004
Claeys 2005	1	100	2	100	2.8%	0.49 [0.04, 5.55]	2005
CLEAR PLATELETS-2 2009	0	98	1	102	2.1%	0.34 [0.01, 8.53]	2009
OPTIMIZE-IT 2009	1	24	1	22	1.4%	0.91 [0.05, 15.54]	2009
Total (95% CI)		**2993**		**2975**	**100.0%**	**0.83 [0.59, 1.17]**	
Total events	60		72				

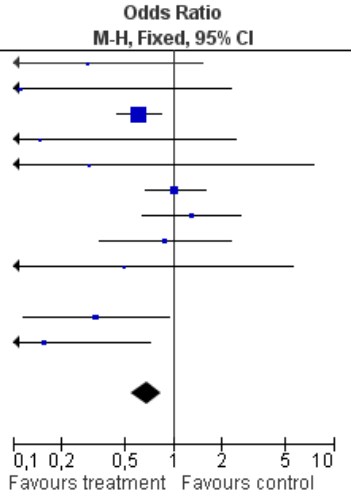
Heterogeneity: Chi² = 2.21, df = 7 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.08 (P = 0.28)



2.3 30-day mortality or myocardial infarction

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Galassi 1999	2	54	6	52	2.9%	0.29 [0.06, 1.53]	1999
Chen 2000	0	22	3	20	1.8%	0.11 [0.01, 2.30]	2000
ESPRIT 2000	67	1040	104	1024	48.9%	0.61 [0.44, 0.84]	2000
PRIDE 2001	1	109	1	17	0.9%	0.15 [0.01, 2.49]	2001
TOPSTAR 2002	0	50	1	46	0.8%	0.30 [0.01, 7.56]	2002
ISAR-REACT 2004	43	1079	42	1080	20.1%	1.03 [0.66, 1.58]	2004
ISAR-SWEET 2004	18	351	14	350	6.6%	1.30 [0.63, 2.65]	2004
Claeys 2005	9	100	10	100	4.5%	0.89 [0.35, 2.29]	2005
Cuisset 2008	1	74	2	75	1.0%	0.50 [0.04, 5.64]	2008
OPTIMIZE-IT 2009	0	24	0	22		Not estimable	2009
3T/2R 2009	5	132	14	131	6.7%	0.33 [0.11, 0.94]	2009
CLEAR PLATELETS-2 2009	2	98	12	102	5.7%	0.16 [0.03, 0.72]	2009
Total (95% CI)		**3133**		**3019**	**100.0%**	**0.68 [0.55, 0.85]**	
Total events	148		209				

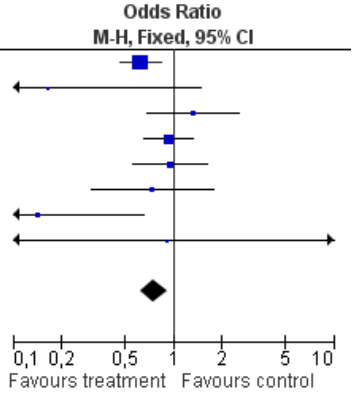
Heterogeneity: Chi² = 16.54, df = 10 (P = 0.09); I² = 40%
Test for overall effect: Z = 3.47 (P = 0.0005)



2.4 6-month mortality or myocardial infarction

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
ESPRIT 2000	78	1040	118	1024	44.3%	0.62 [0.46, 0.84]	2000
TOPSTAR 2002	1	50	5	46	2.1%	0.17 [0.02, 1.49]	2002
ISAR-SMART-2 2004	22	251	17	251	6.2%	1.32 [0.68, 2.55]	2004
ISAR-REACT 2004	65	1079	69	1080	26.1%	0.94 [0.66, 1.33]	2004
ISAR-SWEET 2004	29	351	30	350	11.1%	0.96 [0.56, 1.64]	2004
Claeys 2005	10	100	13	100	4.7%	0.74 [0.31, 1.78]	2005
CLEAR PLATELETS-2 2009	2	98	13	102	5.0%	0.14 [0.03, 0.65]	2009
OPTIMIZE-IT 2009	1	24	1	22	0.4%	0.91 [0.05, 15.54]	2009
Total (95% CI)		**2993**		**2975**	**100.0%**	**0.76 [0.63, 0.92]**	
Total events	208		266				

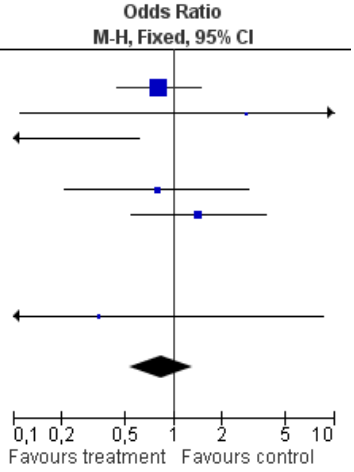
Heterogeneity: Chi² = 13.10, df = 7 (P = 0.07); I² = 47%
Test for overall effect: Z = 2.85 (P = 0.004)



2.5 30-day urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Galassi 1999	0	54	0	52		Not estimable	1999
ESPRIT 2000	20	1040	24	1024	56.7%	0.82 [0.45, 1.49]	2000
Chen 2000	1	22	0	20	1.2%	2.86 [0.11, 74.31]	2000
PRIDE 2001	0	109	2	17	10.2%	0.03 [0.00, 0.62]	2001
TOPSTAR 2002	0	50	0	46		Not estimable	2002
ISAR-SWEET 2004	4	351	5	350	11.8%	0.80 [0.21, 2.99]	2004
ISAR-REACT 2004	10	1079	7	1080	16.6%	1.43 [0.54, 3.78]	2004
Claeys 2005	0	100	0	100		Not estimable	2005
Cuisset 2008	0	74	0	75		Not estimable	2008
OPTIMIZE-IT 2009	0	24	0	22		Not estimable	2009
CLEAR PLATELETS-2 2009	0	98	1	102	3.5%	0.34 [0.01, 8.53]	2009
Total (95% CI)		**3001**		**2888**	**100.0%**	**0.84 [0.54, 1.32]**	
Total events	35		39				

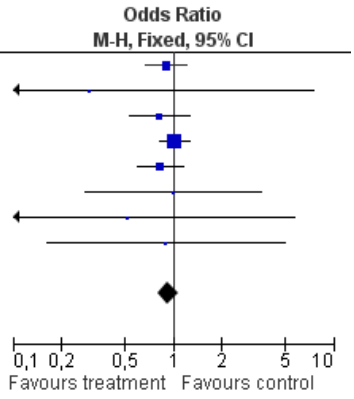
Heterogeneity: Chi² = 6.67, df = 5 (P = 0.25); I² = 25%
Test for overall effect: Z = 0.75 (P = 0.46)



2.6 6-month urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
ESPRIT 2000	89	1040	96	1024	23.2%	0.90 [0.67, 1.22]	2000
TOPSTAR 2002	0	50	1	46	0.4%	0.30 [0.01, 7.56]	2002
ISAR-SMART-2 2004	47	251	55	251	11.7%	0.82 [0.53, 1.27]	2004
ISAR-REACT 2004	208	1079	204	1080	43.1%	1.03 [0.83, 1.27]	2004
ISAR-SWEET 2004	84	351	96	350	19.2%	0.83 [0.59, 1.17]	2004
Claeys 2005	5	100	5	100	1.2%	1.00 [0.28, 3.57]	2005
CLEAR PLATELETS-2 2009	1	98	2	102	0.5%	0.52 [0.05, 5.78]	2009
OPTIMIZE-IT 2009	3	24	3	22	0.7%	0.90 [0.16, 5.03]	2009
Total (95% CI)		**2993**		**2975**	**100.0%**	**0.93 [0.80, 1.07]**	
Total events	437		462				

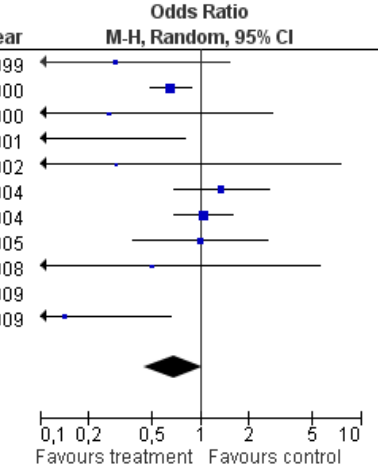
Heterogeneity: Chi² = 2.27, df = 7 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.99 (P = 0.32)



2.7 30-day mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Galassi 1999	2	54	6	52	5.4%	0.29 [0.06, 1.53]	1999
ESPRIT 2000	78	1040	113	1024	26.5%	0.65 [0.48, 0.88]	2000
Chen 2000	1	22	3	20	2.9%	0.27 [0.03, 2.83]	2000
PRIDE 2001	1	109	2	17	2.7%	0.07 [0.01, 0.81]	2001
TOPSTAR 2002	0	50	1	46	1.6%	0.30 [0.01, 7.56]	2002
ISAR-SWEET 2004	20	351	15	350	16.9%	1.35 [0.68, 2.68]	2004
ISAR-REACT 2004	45	1079	43	1080	23.3%	1.05 [0.68, 1.61]	2004
Claeys 2005	9	100	9	100	11.7%	1.00 [0.38, 2.63]	2005
Cuisset 2008	1	74	2	75	2.8%	0.50 [0.04, 5.64]	2008
OPTIMIZE-IT 2009	0	24	0	22		Not estimable	2009
CLEAR PLATELETS-2 2009	2	98	13	102	6.2%	0.14 [0.03, 0.65]	2009
Total (95% CI)		**3001**		**2888**	**100.0%**	**0.68 [0.45, 1.04]**	
Total events	159		207				

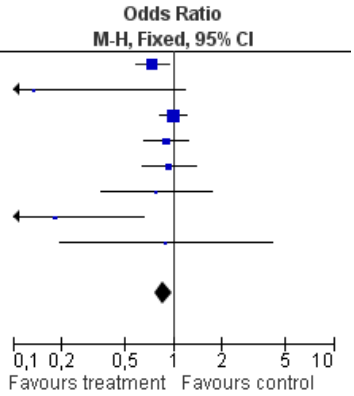
Heterogeneity: Tau² = 0.15; Chi² = 16.93, df = 9 (P = 0.05); I² = 47%
Test for overall effect: Z = 1.79 (P = 0.07)



2.8 6-month mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
ESPRIT 2000	148	1040	187	1024	30.7%	0.74 [0.59, 0.94]	2000
TOPSTAR 2002	1	50	6	46	1.2%	0.14 [0.02, 1.18]	2002
ISAR-REACT 2004	257	1079	257	1080	37.2%	1.00 [0.82, 1.22]	2004
ISAR-SWEET 2004	105	351	112	350	14.9%	0.91 [0.66, 1.25]	2004
ISAR-SMART-2 2004	69	251	72	251	9.9%	0.94 [0.64, 1.39]	2004
Claeys 2005	13	100	16	100	2.6%	0.78 [0.36, 1.73]	2005
CLEAR PLATELETS-2 2009	3	98	15	102	2.7%	0.18 [0.05, 0.65]	2009
OPTIMIZE-IT 2009	4	24	4	22	0.7%	0.90 [0.20, 4.14]	2009
Total (95% CI)		**2993**		**2975**	**100.0%**	**0.86 [0.76, 0.98]**	
Total events	600		669				

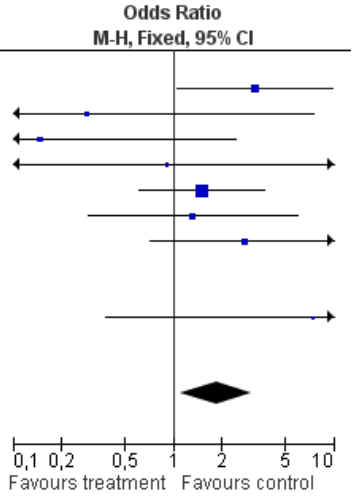
Heterogeneity: Chi² = 12.58, df = 7 (P = 0.08); I² = 44%
Test for overall effect: Z = 2.30 (P = 0.02)



2.9 30-day major bleeding

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Galassi 1999	0	54	0	52		Not estimable	1999
ESPRIT 2000	13	1040	4	1024	17.8%	3.23 [1.05, 9.93]	2000
Chen 2000	0	22	1	20	6.9%	0.29 [0.01, 7.51]	2000
PRIDE 2001	1	109	1	17	7.7%	0.15 [0.01, 2.49]	2001
TOPSTAR 2002	1	50	1	46	4.6%	0.92 [0.06, 15.12]	2002
ISAR-REACT 2004	12	1079	8	1080	35.4%	1.51 [0.61, 3.70]	2004
ISAR-SWEET 2004	4	351	3	350	13.3%	1.33 [0.30, 6.00]	2004
Claeys 2005	8	100	3	100	12.3%	2.81 [0.72, 10.92]	2005
Cuisset 2008	0	74	0	75		Not estimable	2008
OPTIMIZE-IT 2009	0	24	0	22		Not estimable	2009
CLEAR PLATELETS-2 2009	3	98	0	102	2.1%	7.51 [0.38, 147.37]	2009
3T/2R 2009	0	132	0	131		Not estimable	2009
Total (95% CI)		**3133**		**3019**	**100.0%**	**1.86 [1.11, 3.12]**	
Total events	42		21				

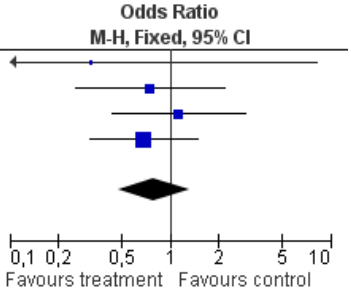
Heterogeneity: Chi² = 7.12, df = 7 (P = 0.42); I² = 2%
Test for overall effect: Z = 2.37 (P = 0.02)



3.1 30-day mortality

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Simoons 1994	0	30	1	30	4.5%	0.32 [0.01, 8.24]	1994
CAPTURE 1997	6	630	8	635	23.8%	0.75 [0.26, 2.18]	1997
RESTORE 1997	9	1071	8	1070	23.9%	1.13 [0.43, 2.93]	1997
ISAR-REACT 2 2006	11	1012	16	1010	47.8%	0.68 [0.32, 1.48]	2006
Total (95% CI)		**2743**		**2745**	**100.0%**	**0.79 [0.47, 1.32]**	
Total events	26		33				

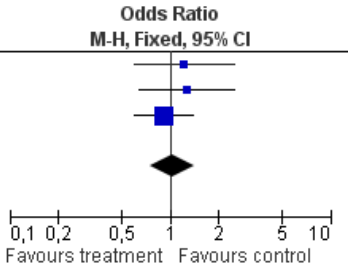
Heterogeneity: Chi² = 0.96, df = 3 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)



3.2 6-month mortality

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
CAPTURE 1997	17	630	14	635	18.0%	1.23 [0.60, 2.52]	1997
RESTORE 1997	19	1070	15	1069	19.6%	1.27 [0.64, 2.51]	1997
ISAR-REACT 2 2006	45	1012	49	1010	62.3%	0.91 [0.60, 1.38]	2006
Total (95% CI)		**2712**		**2714**	**100.0%**	**1.04 [0.76, 1.43]**	
Total events	81		78				

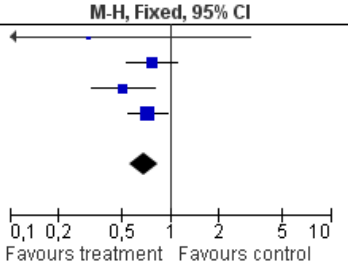
Heterogeneity: Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)



3.3 30-day mortality or myocardial infarction

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Simoons 1994	1	30	3	30	1.3%	0.31 [0.03, 3.17]	1994
RESTORE 1997	54	1071	69	1070	28.7%	0.77 [0.53, 1.11]	1997
CAPTURE 1997	30	630	57	635	23.6%	0.51 [0.32, 0.80]	1997
ISAR-REACT 2 2006	87	1012	116	1010	46.4%	0.72 [0.54, 0.97]	2006
Total (95% CI)		**2743**		**2745**	**100.0%**	**0.68 [0.56, 0.83]**	
Total events	172		245				

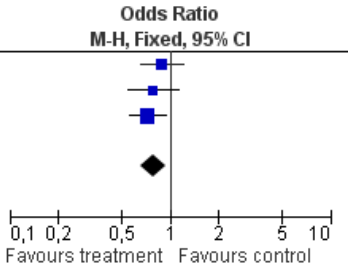
Heterogeneity: Chi² = 2.65, df = 3 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.71 (P = 0.0002)



3.4 6-month mortality or myocardial infarction

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
RESTORE 1997	86	1070	96	1069	30.4%	0.89 [0.65, 1.20]	1997
CAPTURE 1997	58	630	73	635	22.7%	0.78 [0.54, 1.12]	1997
ISAR-REACT 2 2006	117	1012	154	1010	46.9%	0.73 [0.56, 0.94]	2006
Total (95% CI)		**2712**		**2714**	**100.0%**	**0.79 [0.66, 0.94]**	
Total events	261		323				

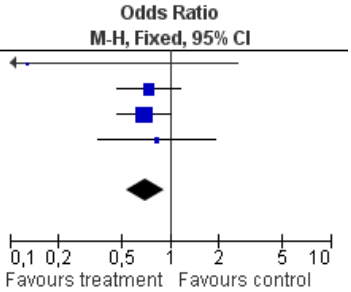
Heterogeneity: Chi² = 0.95, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.71 (P = 0.007)



3.5 30-day urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Simoons 1994	0	30	3	30	2.9%	0.13 [0.01, 2.61]	1994
RESTORE 1997	32	1071	43	1070	34.6%	0.74 [0.46, 1.17]	1997
CAPTURE 1997	49	630	69	635	52.6%	0.69 [0.47, 1.02]	1997
ISAR-REACT 2 2006	10	1012	12	1010	9.9%	0.83 [0.36, 1.93]	2006
Total (95% CI)		**2743**		**2745**	**100.0%**	**0.70 [0.53, 0.93]**	
Total events	91		127				

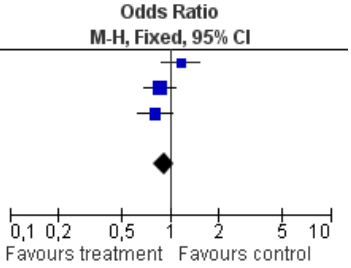
Heterogeneity: Chi² = 1.41, df = 3 (P = 0.70); I² = 0%
Test for overall effect: Z = 2.48 (P = 0.01)



3.6 6-month urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
CAPTURE 1997	135	630	120	635	23.6%	1.17 [0.89, 1.54]	1997
RESTORE 1997	172	1070	194	1069	40.9%	0.86 [0.69, 1.08]	1997
ISAR-REACT 2 2006	137	1012	164	1010	35.6%	0.81 [0.63, 1.03]	2006
Total (95% CI)		**2712**		**2714**	**100.0%**	**0.92 [0.79, 1.06]**	
Total events	444		478				

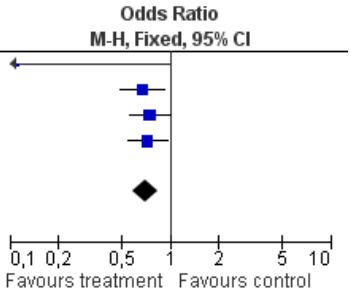
Heterogeneity: Chi² = 4.32, df = 2 (P = 0.12); I² = 54%
Test for overall effect: Z = 1.21 (P = 0.23)



3.7 30-day mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Simoons 1994	1	30	7	30	2.2%	0.11 [0.01, 0.99]	1994
CAPTURE 1997	71	630	101	635	28.9%	0.67 [0.48, 0.93]	1997
RESTORE 1997	86	1071	112	1070	33.4%	0.75 [0.56, 1.00]	1997
ISAR-REACT 2 2006	90	1012	120	1010	35.5%	0.72 [0.54, 0.97]	2006
Total (95% CI)		**2743**		**2745**	**100.0%**	**0.70 [0.59, 0.84]**	
Total events	248		340				

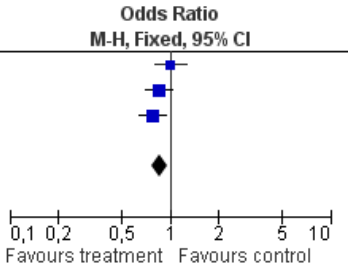
Heterogeneity: Chi² = 3.01, df = 3 (P = 0.39); I² = 0%
Test for overall effect: Z = 3.99 (P < 0.0001)



3.8 6-month mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
CAPTURE 1997	193	630	193	635	23.4%	1.01 [0.80, 1.28]	1997
RESTORE 1997	258	1070	290	1069	38.6%	0.85 [0.70, 1.04]	1997
ISAR-REACT 2 2006	234	1012	281	1010	38.0%	0.78 [0.64, 0.95]	2006
Total (95% CI)		**2712**		**2714**	**100.0%**	**0.86 [0.76, 0.97]**	
Total events	685		764				

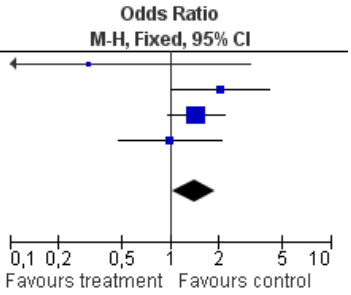
Heterogeneity: Chi² = 2.67, df = 2 (P = 0.26); I² = 25%
Test for overall effect: Z = 2.40 (P = 0.02)



3.9 30-day major bleeding

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Simoons 1994	1	30	3	30	4.4%	0.31 [0.03, 3.17]	1994
CAPTURE 1997	24	630	12	635	17.4%	2.06 [1.02, 4.15]	1997
RESTORE 1997	57	1071	40	1070	57.3%	1.45 [0.96, 2.19]	1997
ISAR-REACT 2 2006	14	1012	14	1010	20.9%	1.00 [0.47, 2.10]	2006
Total (95% CI)		**2743**		**2745**	**100.0%**	**1.41 [1.03, 1.93]**	
Total events	96		69				

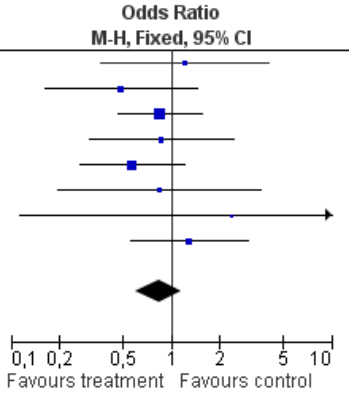
Heterogeneity: Chi² = 3.58, df = 3 (P = 0.31); I² = 16%
Test for overall effect: Z = 2.14 (P = 0.03)



4.1 30-day mortality

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
RAPPORT 1998	6	241	5	242	6.3%	1.21 [0.36, 4.02]	1998
ADMIRAL 2001	5	149	10	151	12.4%	0.49 [0.16, 1.47]	2001
CADILLAC 2002	20	1052	23	1030	29.4%	0.85 [0.46, 1.55]	2002
ACE 2003	7	200	8	200	9.9%	0.87 [0.31, 2.45]	2003
On-TIME 2 2008	11	473	19	477	23.8%	0.57 [0.27, 1.22]	2008
Shen 2008	5	114	3	58	4.9%	0.84 [0.19, 3.65]	2008
JEPPORT 2009	2	635	0	303	0.9%	2.40 [0.11, 50.05]	2009
BRAVE-3 2009	13	401	10	399	12.5%	1.30 [0.56, 3.01]	2009
Total (95% CI)		**3265**		**2860**	**100.0%**	**0.83 [0.60, 1.16]**	
Total events	69		78				

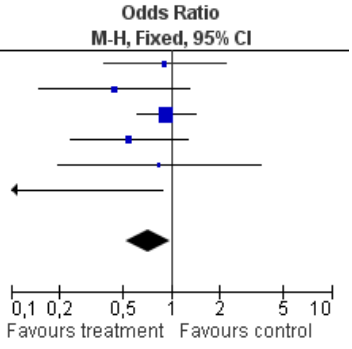
Heterogeneity: Chi² = 3.78, df = 7 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.08 (P = 0.28)



4.2 6-month mortality

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
RAPPORT 1998	10	241	11	242	11.3%	0.91 [0.38, 2.18]	1998
ADMIRAL 2001	5	149	11	151	11.4%	0.44 [0.15, 1.30]	2001
CADILLAC 2002	43	1052	45	1030	47.0%	0.93 [0.61, 1.43]	2002
ACE 2003	9	200	16	200	16.5%	0.54 [0.23, 1.26]	2003
Shen 2008	5	114	3	58	4.1%	0.84 [0.19, 3.65]	2008
Fu 2008	0	72	9	78	9.8%	0.05 [0.00, 0.88]	2008
Total (95% CI)		**1828**		**1759**	**100.0%**	**0.72 [0.53, 0.99]**	
Total events	72		95				

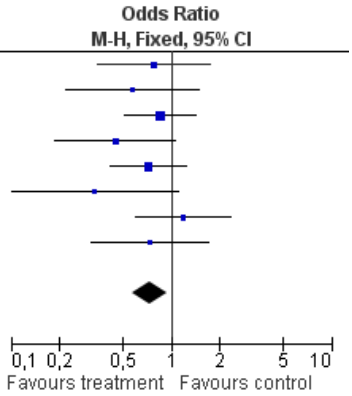
Heterogeneity: Chi² = 6.26, df = 5 (P = 0.28); I² = 20%
Test for overall effect: Z = 2.05 (P = 0.04)



4.3 30-day mortality or myocardial infarction

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
RAPPORT 1998	11	241	14	242	9.5%	0.78 [0.35, 1.75]	1998
ADMIRAL 2001	7	149	12	151	8.1%	0.57 [0.22, 1.49]	2001
CADILLAC 2002	28	1052	32	1030	22.5%	0.85 [0.51, 1.43]	2002
ACE 2003	8	200	17	200	11.7%	0.45 [0.19, 1.06]	2003
On-TIME 2 2008	24	473	33	477	22.3%	0.72 [0.42, 1.24]	2008
Shen 2008	5	114	7	58	6.3%	0.33 [0.10, 1.10]	2008
BRAVE-3 2009	19	401	16	399	10.9%	1.19 [0.60, 2.35]	2009
JEPPORT 2009	14	635	9	303	8.5%	0.74 [0.32, 1.72]	2009
Total (95% CI)		**3265**		**2860**	**100.0%**	**0.74 [0.57, 0.95]**	
Total events	116		140				

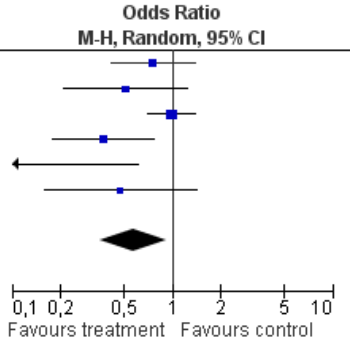
Heterogeneity: Chi² = 5.47, df = 7 (P = 0.60); I² = 0%
Test for overall effect: Z = 2.33 (P = 0.02)



4.4 6-month mortality or myocardial infarction

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
RAPPORT 1998	21	241	27	242	21.6%	0.76 [0.42, 1.39]	1998
ADMIRAL 2001	8	149	15	151	15.4%	0.51 [0.21, 1.25]	2001
CADILLAC 2002	69	1052	68	1030	27.7%	0.99 [0.70, 1.40]	2002
ACE 2003	11	200	27	200	18.6%	0.37 [0.18, 0.77]	2003
Fu 2008	1	72	12	78	4.7%	0.08 [0.01, 0.61]	2008
Shen 2008	7	114	7	58	12.1%	0.48 [0.16, 1.43]	2008
Total (95% CI)		**1828**		**1759**	**100.0%**	**0.57 [0.35, 0.93]**	
Total events	117		156				

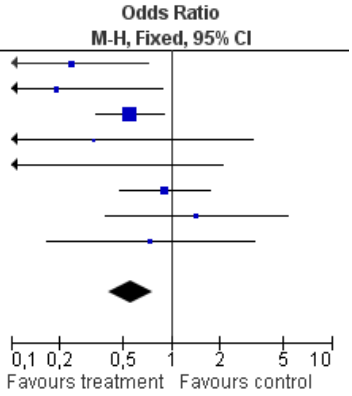
Heterogeneity: Tau² = 0.19; Chi² = 12.11, df = 5 (P = 0.03); I² = 59%
Test for overall effect: Z = 2.26 (P = 0.02)



4.5 30-day urgent revascularisation

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
RAPPORT 1998	4	241	16	242	15.2%	0.24 [0.08, 0.72]	1998
ADMIRAL 2001	2	149	10	151	9.5%	0.19 [0.04, 0.89]	2001
CADILLAC 2002	26	1052	45	1030	42.9%	0.55 [0.34, 0.91]	2002
ACE 2003	1	200	3	200	2.9%	0.33 [0.03, 3.20]	2003
Shen 2008	0	114	2	58	3.2%	0.10 [0.00, 2.09]	2008
On-TIME 2 2008	18	473	20	477	18.6%	0.90 [0.47, 1.73]	2008
JEPPORT 2009	9	635	3	303	3.9%	1.44 [0.39, 5.35]	2009
BRAVE-3 2009	3	401	4	399	3.9%	0.74 [0.17, 3.35]	2009
Total (95% CI)		**3265**		**2860**	**100.0%**	**0.56 [0.40, 0.77]**	
Total events	63		103				

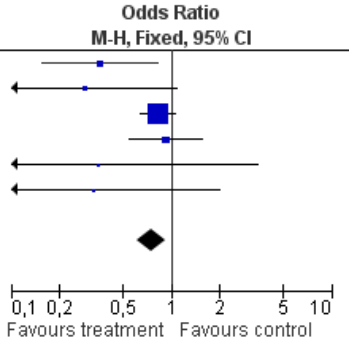
Heterogeneity: Chi² = 9.81, df = 7 (P = 0.20); I² = 29%
Test for overall effect: Z = 3.58 (P = 0.0003)



4.6 6-month urgent revascularisation

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
RAPPORT 1998	8	241	21	242	10.3%	0.36 [0.16, 0.83]	1998
ADMIRAL 2001	3	149	10	151	4.9%	0.29 [0.08, 1.07]	2001
CADILLAC 2002	128	1052	148	1030	66.8%	0.83 [0.64, 1.06]	2002
ACE 2003	32	200	34	200	14.5%	0.93 [0.55, 1.58]	2003
Fu 2008	1	72	3	78	1.4%	0.35 [0.04, 3.46]	2008
Shen 2008	2	114	3	58	2.0%	0.33 [0.05, 2.02]	2008
Total (95% CI)		**1828**		**1759**	**100.0%**	**0.75 [0.61, 0.93]**	
Total events	174		219				

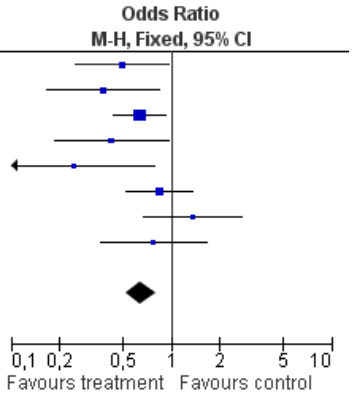
Heterogeneity: Chi² = 7.37, df = 5 (P = 0.19); I² = 32%
Test for overall effect: Z = 2.65 (P = 0.008)



4.7 30-day mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
RAPPORT 1998	14	241	27	242	12.1%	0.49 [0.25, 0.96]	1998
ADMIRAL 2001	9	149	22	151	9.8%	0.38 [0.17, 0.85]	2001
CADILLAC 2002	48	1052	72	1030	33.1%	0.64 [0.44, 0.93]	2002
ACE 2003	9	200	20	200	9.1%	0.42 [0.19, 0.96]	2003
Shen 2008	5	114	9	58	5.4%	0.25 [0.08, 0.78]	2008
On-TIME 2 2008	33	473	39	477	17.2%	0.84 [0.52, 1.36]	2008
BRAVE-3 2009	19	401	14	399	6.4%	1.37 [0.68, 2.77]	2009
JEPPORT 2009	18	635	11	303	6.9%	0.77 [0.36, 1.66]	2009
Total (95% CI)		**3265**		**2860**	**100.0%**	**0.64 [0.52, 0.80]**	
Total events	155		214				

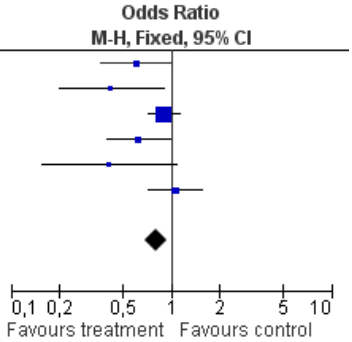
Heterogeneity: Chi² = 11.76, df = 7 (P = 0.11); I² = 40%
Test for overall effect: Z = 4.01 (P < 0.0001)



4.8 6-month mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
RAPPORT 1998	28	241	43	242	11.5%	0.61 [0.36, 1.02]	1998
ADMIRAL 2001	11	149	24	151	6.7%	0.42 [0.20, 0.90]	2001
CADILLAC 2002	178	1052	190	1030	48.5%	0.90 [0.72, 1.13]	2002
ACE 2003	43	200	61	200	14.5%	0.62 [0.40, 0.98]	2003
Shen 2008	9	114	10	58	3.7%	0.41 [0.16, 1.08]	2008
JEPPORT 2009	95	635	43	303	15.0%	1.06 [0.72, 1.57]	2009
Total (95% CI)		**2391**		**1984**	**100.0%**	**0.80 [0.68, 0.94]**	
Total events	364		371				

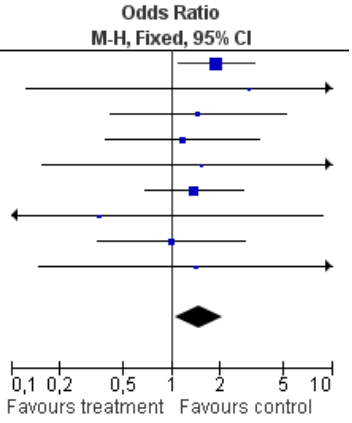
Heterogeneity: Chi² = 9.97, df = 5 (P = 0.08); I² = 50%
Test for overall effect: Z = 2.70 (P = 0.007)



4.9 30-day major bleeding

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
RAPPORT 1998	40	241	23	242	35.6%	1.89 [1.10, 3.28]	1998
ADMIRAL 2001	1	149	0	151	0.9%	3.06 [0.12, 75.73]	2001
CADILLAC 2002	6	1052	4	1030	7.5%	1.47 [0.41, 5.23]	2002
ACE 2003	7	200	6	200	10.8%	1.17 [0.39, 3.55]	2003
Shen 2008	3	114	1	58	2.4%	1.54 [0.16, 15.15]	2008
On-TIME 2 2008	19	473	14	477	24.9%	1.38 [0.69, 2.79]	2008
Fu 2008	0	72	1	78	2.7%	0.36 [0.01, 8.89]	2008
BRAVE-3 2009	7	401	7	399	12.8%	0.99 [0.35, 2.86]	2009
JEPPORT 2009	3	635	1	303	2.5%	1.43 [0.15, 13.84]	2009
Total (95% CI)		**3337**		**2938**	**100.0%**	**1.49 [1.06, 2.11]**	
Total events	86		57				

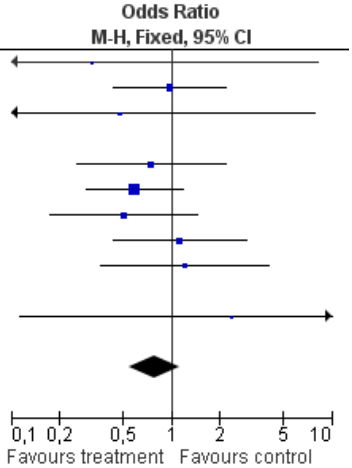
Heterogeneity: Chi² = 2.48, df = 8 (P = 0.96); I² = 0%
Test for overall effect: Z = 2.28 (P = 0.02)



5.1 30-day mortality

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Simoons 1994	0	30	1	30	2.3%	0.32 [0.01, 8.24]	1994
EPIC 1994	12	708	12	696	18.2%	0.98 [0.44, 2.20]	1994
IMPACT 1995	1	101	1	49	2.0%	0.48 [0.03, 7.84]	1995
Kereiakes 1996	0	73	0	20		Not estimable	1996
CAPTURE 1997	6	630	8	635	12.1%	0.75 [0.26, 2.18]	1997
IMPACT-II 1997	18	2682	15	1328	30.5%	0.59 [0.30, 1.18]	1997
EPILOG 1997	7	1853	7	939	14.2%	0.50 [0.18, 1.44]	1997
RESTORE 1997	9	1071	8	1070	12.2%	1.13 [0.43, 2.93]	1997
RAPPORT 1998	6	241	5	242	7.5%	1.21 [0.36, 4.02]	1998
Chen 2000	0	22	0	20		Not estimable	2000
JEPPORT 2009	2	635	0	303	1.0%	2.40 [0.11, 50.05]	2009
Total (95% CI)		**8046**		**5332**	**100.0%**	**0.79 [0.55, 1.14]**	
Total events	61		57				

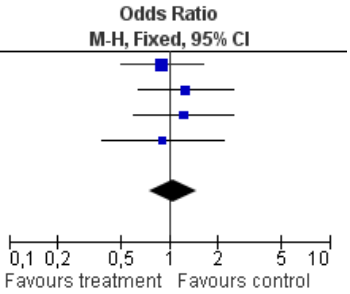
Heterogeneity: Chi² = 3.60, df = 8 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.27 (P = 0.21)



5.2 6-month mortality

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
EPIC 1994	22	708	24	696	37.7%	0.90 [0.50, 1.62]	1994
RESTORE 1997	19	1070	15	1069	23.7%	1.27 [0.64, 2.51]	1997
CAPTURE 1997	17	630	14	635	21.8%	1.23 [0.60, 2.52]	1997
RAPPORT 1998	10	241	11	242	16.9%	0.91 [0.38, 2.18]	1998
Total (95% CI)		**2649**		**2642**	**100.0%**	**1.06 [0.75, 1.50]**	
Total events	68		64				

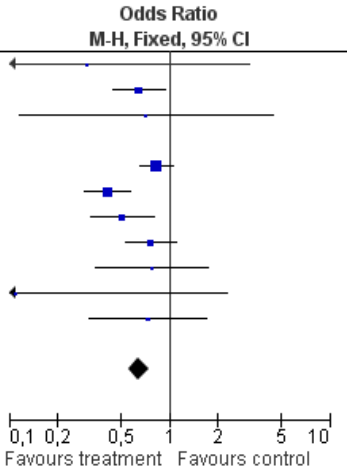
Heterogeneity: Chi² = 0.86, df = 3 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)



5.3 30-day mortality or myocardial infarction

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Simoons 1994	1	30	3	30	0.6%	0.31 [0.03, 3.17]	1994
EPIC 1994	49	708	72	696	14.4%	0.64 [0.44, 0.94]	1994
IMPACT 1995	3	101	2	49	0.6%	0.72 [0.12, 4.45]	1995
Kereiakes 1996	0	73	0	20		Not estimable	1996
IMPACT-II 1997	190	2682	112	1328	29.7%	0.83 [0.65, 1.06]	1997
EPILOG 1997	73	1853	85	939	23.1%	0.41 [0.30, 0.57]	1997
CAPTURE 1997	30	630	57	635	11.5%	0.51 [0.32, 0.80]	1997
RESTORE 1997	54	1071	69	1070	14.0%	0.77 [0.53, 1.11]	1997
RAPPORT 1998	11	241	14	242	2.8%	0.78 [0.35, 1.75]	1998
Chen 2000	0	22	3	20	0.8%	0.11 [0.01, 2.30]	2000
JEPPORT 2009	14	635	9	303	2.5%	0.74 [0.32, 1.72]	2009
Total (95% CI)		**8046**		**5332**	**100.0%**	**0.65 [0.56, 0.75]**	
Total events	425		426				

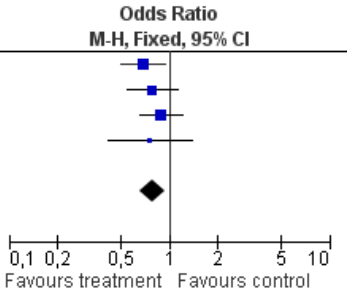
Heterogeneity: Chi² = 15.38, df = 9 (P = 0.08); I² = 41%
Test for overall effect: Z = 6.03 (P < 0.00001)



5.4 6-month mortality or myocardial infarction

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
EPIC 1994	71	708	97	696	33.0%	0.69 [0.50, 0.95]	1994
CAPTURE 1997	58	630	73	635	24.7%	0.78 [0.54, 1.12]	1997
RESTORE 1997	86	1070	96	1069	33.1%	0.89 [0.65, 1.20]	1997
RAPPORT 1998	21	241	27	242	9.2%	0.76 [0.42, 1.39]	1998
Total (95% CI)		**2649**		**2642**	**100.0%**	**0.78 [0.65, 0.94]**	
Total events	236		293				

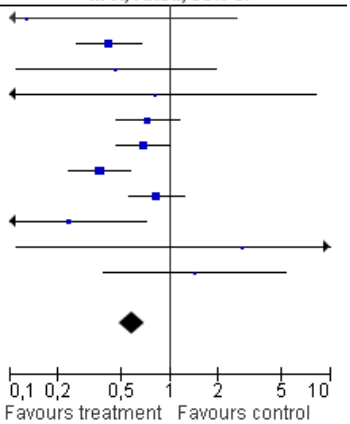
Heterogeneity: Chi² = 1.24, df = 3 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.65 (P = 0.008)



5.5 30-day urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Simoons 1994	0	30	3	30	1.1%	0.13 [0.01, 2.61]	1994
EPIC 1994	27	708	60	696	19.0%	0.42 [0.26, 0.67]	1994
IMPACT 1995	4	101	4	49	1.7%	0.46 [0.11, 1.94]	1995
Kereiakes 1996	3	73	1	20	0.5%	0.81 [0.08, 8.28]	1996
RESTORE 1997	32	1071	43	1070	13.6%	0.74 [0.46, 1.17]	1997
CAPTURE 1997	49	630	69	635	20.6%	0.69 [0.47, 1.02]	1997
EPILOG 1997	36	1853	48	939	20.4%	0.37 [0.24, 0.57]	1997
IMPACT-II 1997	66	2682	39	1328	16.6%	0.83 [0.56, 1.25]	1997
RAPPORT 1998	4	241	16	242	5.1%	0.24 [0.08, 0.72]	1998
Chen 2000	1	22	0	20	0.2%	2.86 [0.11, 74.31]	2000
JEPPORT 2009	9	635	3	303	1.3%	1.44 [0.39, 5.35]	2009
Total (95% CI)		**8046**		**5332**	**100.0%**	**0.58 [0.49, 0.70]**	
Total events	231		286				

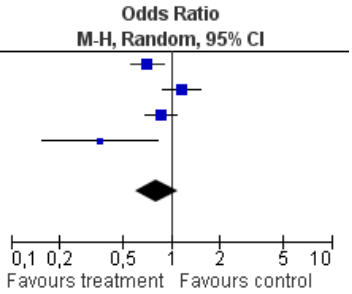
Heterogeneity: Chi² = 17.24, df = 10 (P = 0.07); I² = 42%
Test for overall effect: Z = 5.84 (P < 0.00001)



5.6 6-month urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
EPIC 1994	161	708	205	696	30.4%	0.70 [0.55, 0.90]	1994
CAPTURE 1997	135	630	120	635	28.7%	1.17 [0.89, 1.54]	1997
RESTORE 1997	172	1070	194	1069	31.1%	0.86 [0.69, 1.08]	1997
RAPPORT 1998	8	241	21	242	9.8%	0.36 [0.16, 0.83]	1998
Total (95% CI)		**2649**		**2642**	**100.0%**	**0.81 [0.60, 1.10]**	
Total events	476		540				

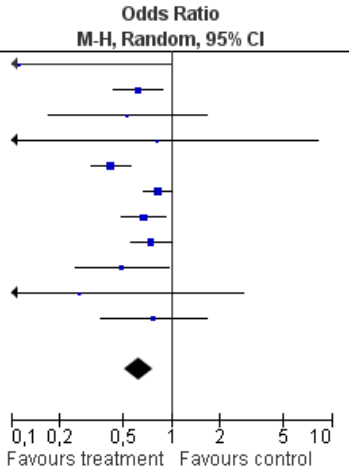
Heterogeneity: Tau² = 0.06; Chi² = 11.59, df = 3 (P = 0.009); I² = 74%
Test for overall effect: Z = 1.33 (P = 0.18)



5.7 30-day mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Simoons 1994	1	30	7	30	0.8%	0.11 [0.01, 0.99]	1994
EPIC 1994	59	708	89	696	14.5%	0.62 [0.44, 0.88]	1994
IMPACT 1995	7	101	6	49	2.7%	0.53 [0.17, 1.68]	1995
Kereiakes 1996	3	73	1	20	0.7%	0.81 [0.08, 8.28]	1996
EPILOG 1997	97	1853	109	939	16.9%	0.42 [0.32, 0.56]	1997
IMPACT-II 1997	256	2682	151	1328	19.9%	0.82 [0.66, 1.02]	1997
CAPTURE 1997	71	630	101	635	15.3%	0.67 [0.48, 0.93]	1997
RESTORE 1997	86	1071	112	1070	16.5%	0.75 [0.56, 1.00]	1997
RAPPORT 1998	14	241	27	242	6.6%	0.49 [0.25, 0.96]	1998
Chen 2000	1	22	3	20	0.7%	0.27 [0.03, 2.83]	2000
JEPPORT 2009	18	635	11	303	5.4%	0.77 [0.36, 1.66]	2009
Total (95% CI)		**8046**		**5332**	**100.0%**	**0.63 [0.51, 0.76]**	
Total events	613		617				

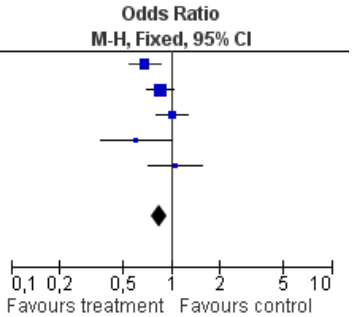
Heterogeneity: Tau² = 0.04; Chi² = 18.62, df = 10 (P = 0.05); I² = 46%
Test for overall effect: Z = 4.60 (P < 0.00001)



5.8 6-month mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
EPIC 1994	191	708	244	696	29.0%	0.68 [0.55, 0.86]	1994
RESTORE 1997	258	1070	290	1069	35.5%	0.85 [0.70, 1.04]	1997
CAPTURE 1997	193	630	193	635	21.5%	1.01 [0.80, 1.28]	1997
RAPPORT 1998	28	241	43	242	6.1%	0.61 [0.36, 1.02]	1998
JEPPORT 2009	95	635	43	303	8.0%	1.06 [0.72, 1.57]	2009
Total (95% CI)		**3284**		**2945**	**100.0%**	**0.84 [0.75, 0.94]**	
Total events	765		813				

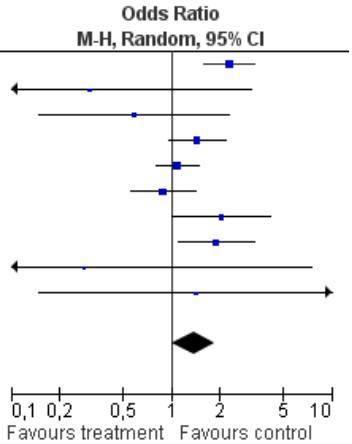
Heterogeneity: Chi² = 8.38, df = 4 (P = 0.08); I² = 52%
Test for overall effect: Z = 2.94 (P = 0.003)



5.9 30-day major bleeding

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
EPIC 1994	99	708	46	696	17.6%	2.30 [1.59, 3.31]	1994
Simoons 1994	1	30	3	30	1.6%	0.31 [0.03, 3.17]	1994
IMPACT 1995	5	101	4	49	4.0%	0.59 [0.15, 2.29]	1995
RESTORE 1997	57	1071	40	1070	16.4%	1.45 [0.96, 2.19]	1997
IMPACT-II 1997	132	2682	60	1328	19.0%	1.09 [0.80, 1.50]	1997
EPILOG 1997	51	1853	29	939	15.2%	0.89 [0.56, 1.41]	1997
CAPTURE 1997	24	630	12	635	10.4%	2.06 [1.02, 4.15]	1997
RAPPORT 1998	40	241	23	242	13.3%	1.89 [1.10, 3.28]	1998
Chen 2000	0	22	1	20	0.8%	0.29 [0.01, 7.51]	2000
JEPPORT 2009	3	635	1	303	1.6%	1.43 [0.15, 13.84]	2009
Total (95% CI)		**7973**		**5312**	**100.0%**	**1.38 [1.02, 1.86]**	
Total events	412		219				

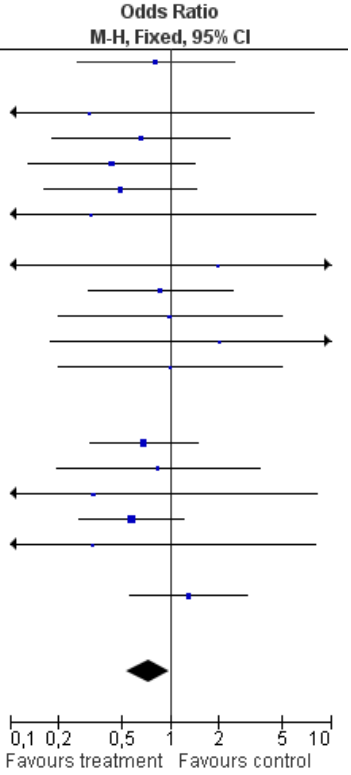
Heterogeneity: Tau² = 0.10; Chi² = 19.55, df = 9 (P = 0.02); I² = 54%
Test for overall effect: Z = 2.10 (P = 0.04)



6.1 30-day mortality

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
EPISTENT 1998	8	1590	5	809	6.6%	0.81 [0.27, 2.49]	1998
ERASER 1999	0	154	0	71		Not estimable	1999
Galassi 1999	0	54	1	52	1.5%	0.31 [0.01, 7.91]	1999
ESPRIT 2000	4	1040	6	1024	6.0%	0.66 [0.18, 2.33]	2000
ISAR-2 2000	4	201	9	200	8.8%	0.43 [0.13, 1.42]	2000
ADMIRAL 2001	5	149	10	151	9.6%	0.49 [0.16, 1.47]	2001
Tamburino 2002	0	54	1	53	1.5%	0.32 [0.01, 8.06]	2002
TOPSTAR 2002	0	50	0	46		Not estimable	2002
Juergens 2002	1	536	0	358	0.6%	2.01 [0.08, 49.44]	2002
ACE 2003	7	200	8	200	7.7%	0.87 [0.31, 2.45]	2003
ISAR-SWEET 2004	3	351	3	350	3.0%	1.00 [0.20, 4.97]	2004
ADVANCE 2004	2	101	1	101	1.0%	2.02 [0.18, 22.64]	2004
ISAR-REACT 2004	3	1079	3	1080	3.0%	1.00 [0.20, 4.97]	2004
Claeys 2005	0	100	0	100		Not estimable	2005
ASIAD 2005	0	128	0	126		Not estimable	2005
ISAR-REACT 2 2006	11	1012	16	1010	15.8%	0.68 [0.32, 1.48]	2006
Shen 2008	5	114	3	58	3.8%	0.84 [0.19, 3.65]	2008
Cuisset 2008	0	74	1	75	1.5%	0.33 [0.01, 8.32]	2008
On-TIME 2 2008	11	473	19	477	18.5%	0.57 [0.27, 1.22]	2008
3T/2R 2009	0	132	1	131	1.5%	0.33 [0.01, 8.13]	2009
CLEAR PLATELETS-2 2009	0	98	0	102		Not estimable	2009
BRAVE-3 2009	13	401	10	399	9.7%	1.30 [0.56, 3.01]	2009
OPTIMIZE-IT 2009	0	24	0	22		Not estimable	2009
Total (95% CI)		**8115**		**6995**	**100.0%**	**0.73 [0.54, 0.98]**	
Total events	77		97				

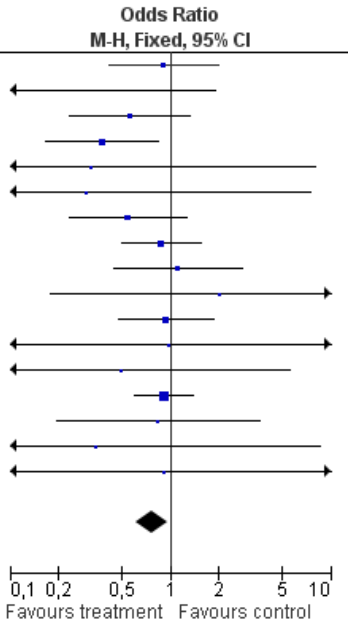
Heterogeneity: Chi² = 6.07, df = 16 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)



6.2 6-month mortality

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
EPISTENT 1998	18	1590	10	809	7.4%	0.91 [0.42, 1.99]	1998
ERASER 1999	0	154	2	71	1.9%	0.09 [0.00, 1.90]	1999
ESPRIT 2000	8	1040	14	1024	7.9%	0.56 [0.23, 1.34]	2000
ADMIRAL 2001	9	149	22	151	11.6%	0.38 [0.17, 0.85]	2001
Tamburino 2002	0	54	1	53	0.8%	0.32 [0.01, 8.06]	2002
TOPSTAR 2002	0	50	1	46	0.9%	0.30 [0.01, 7.56]	2002
ACE 2003	9	200	16	200	8.6%	0.54 [0.23, 1.26]	2003
ISAR-REACT 2004	23	1079	26	1080	14.3%	0.88 [0.50, 1.56]	2004
ISAR-SMART-2 2004	10	251	9	251	4.9%	1.12 [0.45, 2.79]	2004
ADVANCE 2004	2	101	1	101	0.6%	2.02 [0.18, 22.64]	2004
ISAR-SWEET 2004	17	351	18	350	9.7%	0.94 [0.48, 1.85]	2004
ASIAD 2005	1	128	1	126	0.6%	0.98 [0.06, 15.91]	2005
Claeys 2005	1	100	2	100	1.1%	0.49 [0.04, 5.55]	2005
ISAR-REACT 2 2006	45	1012	49	1010	26.4%	0.91 [0.60, 1.38]	2006
Shen 2008	5	114	3	58	2.1%	0.84 [0.19, 3.65]	2008
CLEAR PLATELETS-2 2009	0	98	1	102	0.8%	0.34 [0.01, 8.53]	2009
OPTIMIZE-IT 2009	1	24	1	22	0.6%	0.91 [0.05, 15.54]	2009
Total (95% CI)		**6495**		**5554**	**100.0%**	**0.77 [0.62, 0.96]**	
Total events	149		177				

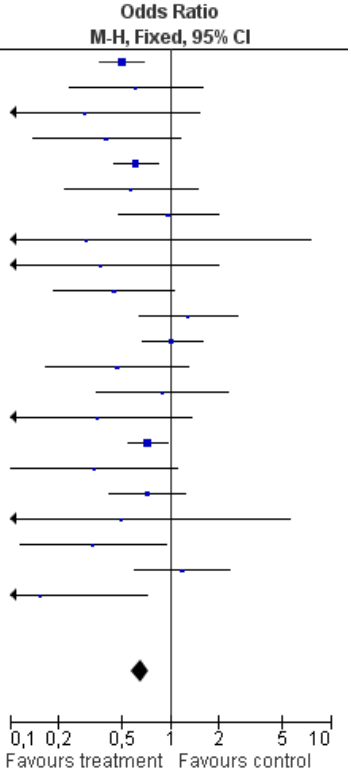
Heterogeneity: Chi² = 9.73, df = 16 (P = 0.88); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)



6.3 30-day mortality or myocardial infarction

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
EPISTENT 1998	86	1590	83	809	18.9%	0.50 [0.37, 0.68]	1998
ERASER 1999	11	154	8	71	1.9%	0.61 [0.23, 1.58]	1999
Galassi 1999	2	54	6	52	1.1%	0.29 [0.06, 1.53]	1999
ISAR-2 2000	5	201	12	200	2.1%	0.40 [0.14, 1.16]	2000
ESPRIT 2000	67	1040	104	1024	17.8%	0.61 [0.44, 0.84]	2000
ADMIRAL 2001	7	149	12	151	2.1%	0.57 [0.22, 1.49]	2001
Juergens 2002	19	536	13	358	2.7%	0.98 [0.48, 2.00]	2002
TOPSTAR 2002	0	50	1	46	0.3%	0.30 [0.01, 7.56]	2002
Tamburino 2002	2	54	5	53	0.9%	0.37 [0.07, 1.99]	2002
ACE 2003	8	200	17	200	3.0%	0.45 [0.19, 1.06]	2003
ISAR-SWEET 2004	18	351	14	350	2.4%	1.30 [0.63, 2.65]	2004
ISAR-REACT 2004	43	1079	42	1080	7.3%	1.03 [0.66, 1.58]	2004
ADVANCE 2004	6	101	12	101	2.1%	0.47 [0.17, 1.30]	2004
Claeys 2005	9	100	10	100	1.7%	0.89 [0.35, 2.29]	2005
ASIAD 2005	3	128	8	126	1.4%	0.35 [0.09, 1.37]	2005
ISAR-REACT 2 2006	87	1012	116	1010	19.3%	0.72 [0.54, 0.97]	2006
Shen 2008	5	114	7	58	1.6%	0.33 [0.10, 1.10]	2008
On-TIME 2 2008	24	473	33	477	5.7%	0.72 [0.42, 1.24]	2008
Cuisset 2008	1	74	2	75	0.4%	0.50 [0.04, 5.64]	2008
3T/2R 2009	5	132	14	131	2.5%	0.33 [0.11, 0.94]	2009
BRAVE-3 2009	19	401	16	399	2.8%	1.19 [0.60, 2.35]	2009
CLEAR PLATELETS-2 2009	2	98	12	102	2.1%	0.16 [0.03, 0.72]	2009
OPTIMIZE-IT 2009	0	24	0	22		Not estimable	2009
Total (95% CI)		**8115**		**6995**	**100.0%**	**0.65 [0.57, 0.74]**	
Total events	429		547				

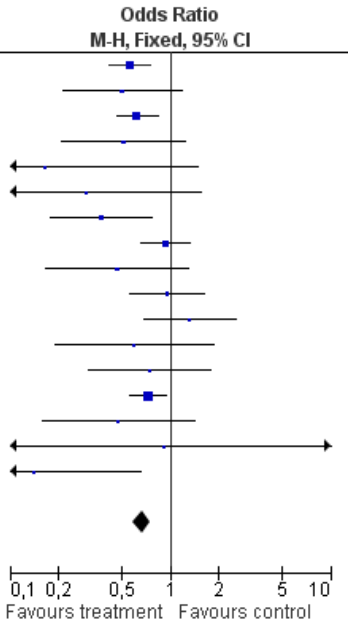
Heterogeneity: Chi² = 26.54, df = 21 (P = 0.19); I² = 21%
Test for overall effect: Z = 6.38 (P < 0.00001)



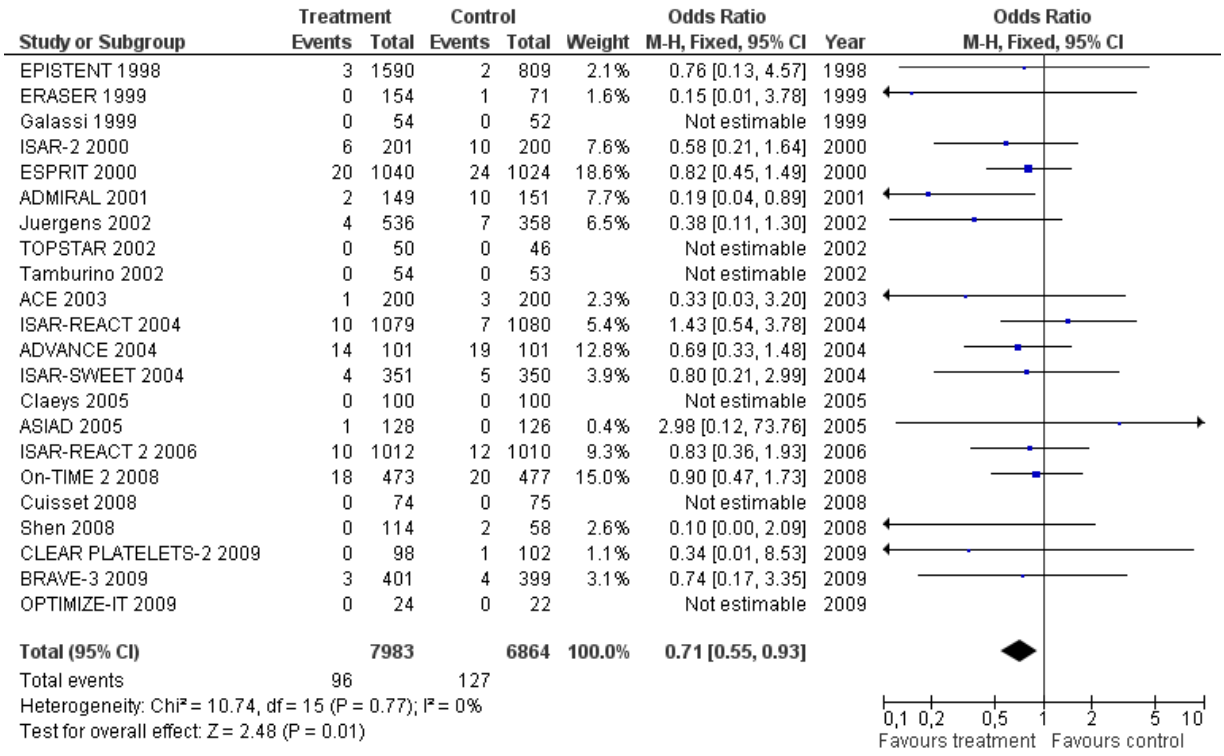
6.4 6-month mortality or myocardial infarction

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
EPISTENT 1998	106	1590	92	809	19.4%	0.56 [0.42, 0.75]	1998
ERASER 1999	13	154	11	71	2.4%	0.50 [0.21, 1.19]	1999
ESPRIT 2000	78	1040	118	1024	18.8%	0.62 [0.46, 0.84]	2000
ADMIRAL 2001	8	149	15	151	2.4%	0.51 [0.21, 1.25]	2001
TOPSTAR 2002	1	50	5	46	0.9%	0.17 [0.02, 1.49]	2002
Tamburino 2002	2	54	6	53	1.0%	0.30 [0.06, 1.57]	2002
ACE 2003	11	200	27	200	4.4%	0.37 [0.18, 0.77]	2003
ISAR-REACT 2004	65	1079	69	1080	11.1%	0.94 [0.66, 1.33]	2004
ADVANCE 2004	6	101	12	101	1.9%	0.47 [0.17, 1.30]	2004
ISAR-SWEET 2004	29	351	30	350	4.7%	0.96 [0.56, 1.64]	2004
ISAR-SMART-2 2004	22	251	17	251	2.6%	1.32 [0.68, 2.55]	2004
ASIAD 2005	5	128	8	126	1.3%	0.60 [0.19, 1.89]	2005
Claeys 2005	10	100	13	100	2.0%	0.74 [0.31, 1.78]	2005
ISAR-REACT 2 2006	117	1012	154	1010	23.3%	0.73 [0.56, 0.94]	2006
Shen 2008	7	114	7	58	1.5%	0.48 [0.16, 1.43]	2008
OPTIMIZE-IT 2009	1	24	1	22	0.2%	0.91 [0.05, 15.54]	2009
CLEAR PLATELETS-2 2009	2	98	13	102	2.1%	0.14 [0.03, 0.65]	2009
Total (95% CI)		**6495**		**5554**	**100.0%**	**0.67 [0.59, 0.76]**	
Total events	483		598				

Heterogeneity: Chi² = 22.25, df = 16 (P = 0.14); I² = 28%
Test for overall effect: Z = 6.25 (P < 0.00001)



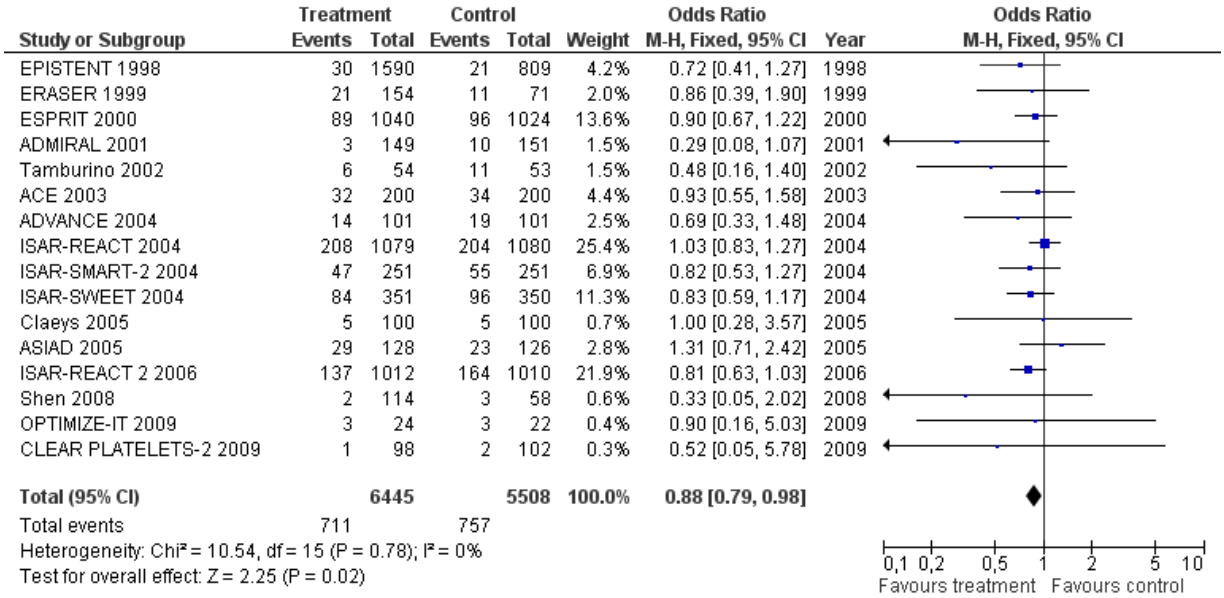
6.5 30-day urgent revascularisation



Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
EPISTENT 1998	3	1590	2	809	2.1%	0.76 [0.13, 4.57]	1998
ERASER 1999	0	154	1	71	1.6%	0.15 [0.01, 3.78]	1999
Galassi 1999	0	54	0	52		Not estimable	1999
ISAR-2 2000	6	201	10	200	7.6%	0.58 [0.21, 1.64]	2000
ESPRIT 2000	20	1040	24	1024	18.6%	0.82 [0.45, 1.49]	2000
ADMIRAL 2001	2	149	10	151	7.7%	0.19 [0.04, 0.89]	2001
Juergens 2002	4	536	7	358	6.5%	0.38 [0.11, 1.30]	2002
TOPSTAR 2002	0	50	0	46		Not estimable	2002
Tamburino 2002	0	54	0	53		Not estimable	2002
ACE 2003	1	200	3	200	2.3%	0.33 [0.03, 3.20]	2003
ISAR-REACT 2004	10	1079	7	1080	5.4%	1.43 [0.54, 3.78]	2004
ADVANCE 2004	14	101	19	101	12.8%	0.69 [0.33, 1.48]	2004
ISAR-SWEET 2004	4	351	5	350	3.9%	0.80 [0.21, 2.99]	2004
Claeys 2005	0	100	0	100		Not estimable	2005
ASIAD 2005	1	128	0	126	0.4%	2.98 [0.12, 73.76]	2005
ISAR-REACT 2 2006	10	1012	12	1010	9.3%	0.83 [0.36, 1.93]	2006
On-TIME 2 2008	18	473	20	477	15.0%	0.90 [0.47, 1.73]	2008
Cuisset 2008	0	74	0	75		Not estimable	2008
Shen 2008	0	114	2	58	2.6%	0.10 [0.00, 2.09]	2008
CLEAR PLATELETS-2 2009	0	98	1	102	1.1%	0.34 [0.01, 8.53]	2009
BRAVE-3 2009	3	401	4	399	3.1%	0.74 [0.17, 3.35]	2009
OPTIMIZE-IT 2009	0	24	0	22		Not estimable	2009
Total (95% CI)		**7983**		**6864**	**100.0%**	**0.71 [0.55, 0.93]**	
Total events	96		127				

Heterogeneity: Chi² = 10.74, df = 15 (P = 0.77); I² = 0%
Test for overall effect: Z = 2.48 (P = 0.01)

6.6 6-month urgent revascularisation



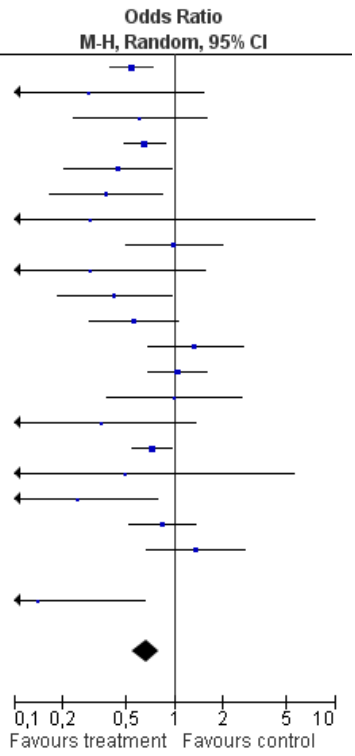
Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
EPISTENT 1998	30	1590	21	809	4.2%	0.72 [0.41, 1.27]	1998
ERASER 1999	21	154	11	71	2.0%	0.86 [0.39, 1.90]	1999
ESPRIT 2000	89	1040	96	1024	13.6%	0.90 [0.67, 1.22]	2000
ADMIRAL 2001	3	149	10	151	1.5%	0.29 [0.08, 1.07]	2001
Tamburino 2002	6	54	11	53	1.5%	0.48 [0.16, 1.40]	2002
ACE 2003	32	200	34	200	4.4%	0.93 [0.55, 1.58]	2003
ADVANCE 2004	14	101	19	101	2.5%	0.69 [0.33, 1.48]	2004
ISAR-REACT 2004	208	1079	204	1080	25.4%	1.03 [0.83, 1.27]	2004
ISAR-SMART-2 2004	47	251	55	251	6.9%	0.82 [0.53, 1.27]	2004
ISAR-SWEET 2004	84	351	96	350	11.3%	0.83 [0.59, 1.17]	2004
Claeys 2005	5	100	5	100	0.7%	1.00 [0.28, 3.57]	2005
ASIAD 2005	29	128	23	126	2.8%	1.31 [0.71, 2.42]	2005
ISAR-REACT 2 2006	137	1012	164	1010	21.9%	0.81 [0.63, 1.03]	2006
Shen 2008	2	114	3	58	0.6%	0.33 [0.05, 2.02]	2008
OPTIMIZE-IT 2009	3	24	3	22	0.4%	0.90 [0.16, 5.03]	2009
CLEAR PLATELETS-2 2009	1	98	2	102	0.3%	0.52 [0.05, 5.78]	2009
Total (95% CI)		**6445**		**5508**	**100.0%**	**0.88 [0.79, 0.98]**	
Total events	711		757				

Heterogeneity: Chi² = 10.54, df = 15 (P = 0.78); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)

6.7 30-day mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
EPISTENT 1998	97	1590	87	809	11.5%	0.54 [0.40, 0.73]	1998
Galassi 1999	2	54	6	52	1.2%	0.29 [0.06, 1.53]	1999
ERASER 1999	11	154	8	71	3.1%	0.61 [0.23, 1.58]	1999
ESPRIT 2000	78	1040	113	1024	11.6%	0.65 [0.48, 0.88]	2000
ISAR-2 2000	10	201	21	200	4.3%	0.45 [0.20, 0.97]	2000
ADMIRAL 2001	9	149	22	151	4.1%	0.38 [0.17, 0.85]	2001
TOPSTAR 2002	0	50	1	46	0.3%	0.30 [0.01, 7.56]	2002
Juergens 2002	21	536	14	358	5.1%	1.00 [0.50, 2.00]	2002
Tamburino 2002	2	54	6	53	1.2%	0.30 [0.06, 1.57]	2002
ACE 2003	9	200	20	200	4.0%	0.42 [0.19, 0.96]	2003
ADVANCE 2004	20	101	31	101	5.6%	0.56 [0.29, 1.06]	2004
ISAR-SWEET 2004	20	351	15	350	5.2%	1.35 [0.68, 2.68]	2004
ISAR-REACT 2004	45	1079	43	1080	8.9%	1.05 [0.68, 1.61]	2004
Claeys 2005	9	100	9	100	3.1%	1.00 [0.38, 2.63]	2005
ASIAD 2005	3	128	8	126	1.7%	0.35 [0.09, 1.37]	2005
ISAR-REACT 2 2006	90	1012	120	1010	11.9%	0.72 [0.54, 0.97]	2006
Cuisset 2008	1	74	2	75	0.6%	0.50 [0.04, 5.64]	2008
Shen 2008	5	114	9	58	2.3%	0.25 [0.08, 0.78]	2008
On-TIME 2 2008	33	473	39	477	7.9%	0.84 [0.52, 1.36]	2008
BRAVE-3 2009	19	401	14	399	5.0%	1.37 [0.68, 2.77]	2009
OPTIMIZE-IT 2009	0	24	0	22		Not estimable	2009
CLEAR PLATELETS-2 2009	2	98	13	102	1.4%	0.14 [0.03, 0.65]	2009
Total (95% CI)		**7983**		**6864**	**100.0%**	**0.66 [0.55, 0.80]**	
Total events	486		601				

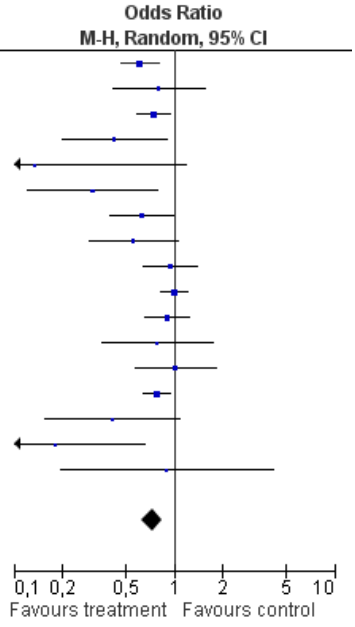
Heterogeneity: Tau² = 0.06; Chi² = 31.69, df = 20 (P = 0.05); I² = 37%
Test for overall effect: Z = 4.26 (P < 0.0001)



6.8 6-month mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
EPISTENT 1998	124	1590	98	809	10.8%	0.61 [0.46, 0.81]	1998
ERASER 1999	33	154	18	71	4.0%	0.80 [0.42, 1.55]	1999
ESPRIT 2000	148	1040	187	1024	12.1%	0.74 [0.59, 0.94]	2000
ADMIRAL 2001	11	149	24	151	3.2%	0.42 [0.20, 0.90]	2001
TOPSTAR 2002	1	50	6	46	0.5%	0.14 [0.02, 1.18]	2002
Tamburino 2002	8	54	19	53	2.2%	0.31 [0.12, 0.79]	2002
ACE 2003	43	200	61	200	6.7%	0.62 [0.40, 0.98]	2003
ADVANCE 2004	20	101	31	101	4.1%	0.56 [0.29, 1.06]	2004
ISAR-SMART-2 2004	69	251	72	251	8.0%	0.94 [0.64, 1.39]	2004
ISAR-REACT 2004	257	1079	257	1079	13.3%	1.00 [0.82, 1.22]	2004
ISAR-SWEET 2004	105	351	112	350	9.7%	0.91 [0.66, 1.25]	2004
Claeys 2005	13	100	16	100	3.0%	0.78 [0.36, 1.73]	2005
ASIAD 2005	29	128	28	126	4.7%	1.03 [0.57, 1.85]	2005
ISAR-REACT 2 2006	234	1012	281	1010	13.2%	0.78 [0.64, 0.95]	2006
Shen 2008	9	114	10	58	2.1%	0.41 [0.16, 1.08]	2008
CLEAR PLATELETS-2 2009	3	98	15	102	1.3%	0.18 [0.05, 0.65]	2009
OPTIMIZE-IT 2009	4	24	4	22	0.9%	0.90 [0.20, 4.14]	2009
Total (95% CI)		**6495**		**5553**	**100.0%**	**0.73 [0.63, 0.85]**	
Total events	1111		1239				

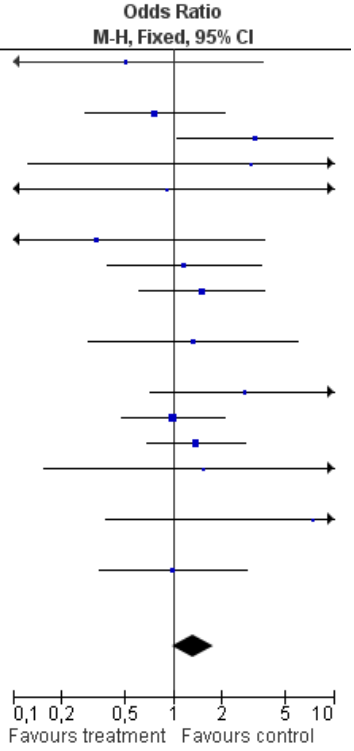
Heterogeneity: Tau² = 0.03; Chi² = 29.08, df = 16 (P = 0.02); I² = 45%
Test for overall effect: Z = 4.07 (P < 0.0001)



6.9 30-day major bleeding

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
EPISTENT 1998	2	1590	2	809	3.6%	0.51 [0.07, 3.61]	1998
Galassi 1999	0	54	0	52		Not estimable	1999
ISAR-2 2000	7	201	9	200	11.7%	0.77 [0.28, 2.10]	2000
ESPRIT 2000	13	1040	4	1024	5.3%	3.23 [1.05, 9.93]	2000
ADMIRAL 2001	1	149	0	151	0.7%	3.06 [0.12, 75.73]	2001
TOPSTAR 2002	1	50	1	46	1.4%	0.92 [0.06, 15.12]	2002
Tamburino 2002	0	54	0	53		Not estimable	2002
Juergens 2002	1	536	2	358	3.2%	0.33 [0.03, 3.68]	2002
ACE 2003	7	200	6	200	7.8%	1.17 [0.39, 3.55]	2003
ISAR-REACT 2004	12	1079	8	1080	10.6%	1.51 [0.61, 3.70]	2004
ADVANCE 2004	0	101	0	101		Not estimable	2004
ISAR-SWEET 2004	4	351	3	350	4.0%	1.33 [0.30, 6.00]	2004
ASIAD 2005	0	128	0	126		Not estimable	2005
Claeys 2005	8	100	3	100	3.7%	2.81 [0.72, 10.92]	2005
ISAR-REACT 2 2006	14	1012	14	1010	18.5%	1.00 [0.47, 2.10]	2006
On-TIME 2 2008	19	473	14	477	18.0%	1.38 [0.69, 2.79]	2008
Shen 2008	3	114	1	58	1.7%	1.54 [0.16, 15.15]	2008
Cuisset 2008	0	74	0	75		Not estimable	2008
CLEAR PLATELETS-2 2009	3	98	0	102	0.6%	7.51 [0.38, 147.37]	2009
OPTIMIZE-IT 2009	0	24	0	22		Not estimable	2009
BRAVE-3 2009	7	401	7	399	9.3%	0.99 [0.35, 2.86]	2009
3T/2R 2009	0	132	0	131		Not estimable	2009
Total (95% CI)		**7961**		**6924**	**100.0%**	**1.33 [0.99, 1.80]**	
Total events	102		74				

Heterogeneity: Chi² = 9.55, df = 14 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.87 (P = 0.06)



7.1 30-day mortality

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
7.1.1 Patients with ACS							
ADVANCE 2004	2	101	1	101	1.8%	2.02 [0.18, 22.64]	2004
ISAR-REACT 2 2006	11	1012	16	1010	28.9%	0.68 [0.32, 1.48]	2006
On-TIME 2 2008	11	473	19	477	33.7%	0.57 [0.27, 1.22]	2008
Shen 2008	5	114	3	58	6.9%	0.84 [0.19, 3.65]	2008
BRAVE-3 2009	13	401	10	399	17.7%	1.30 [0.56, 3.01]	2009
Subtotal (95% CI)		**2101**		**2045**	**89.1%**	**0.80 [0.53, 1.22]**	
Total events	42		49				

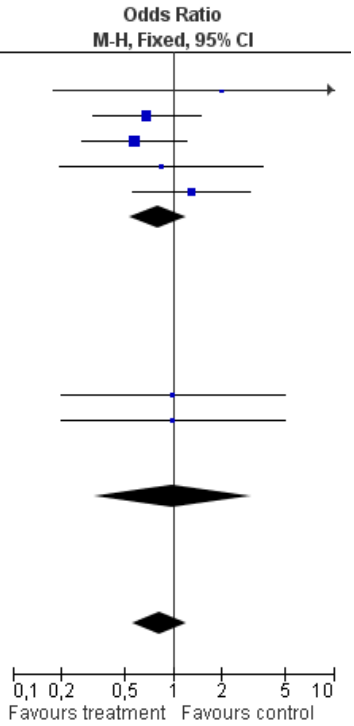
Heterogeneity: Chi² = 2.78, df = 4 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.02 (P = 0.31)

7.1.2 Patients without ACS							
TOPSTAR 2002	0	50	0	46		Not estimable	2002
ISAR-REACT 2004	3	1079	3	1080	5.5%	1.00 [0.20, 4.97]	2004
ISAR-SWEET 2004	3	351	3	350	5.4%	1.00 [0.20, 4.97]	2004
Claeys 2005	0	100	0	100		Not estimable	2005
ASIAD 2005	0	128	0	126		Not estimable	2005
Subtotal (95% CI)		**1708**		**1702**	**10.9%**	**1.00 [0.32, 3.11]**	
Total events	6		6				

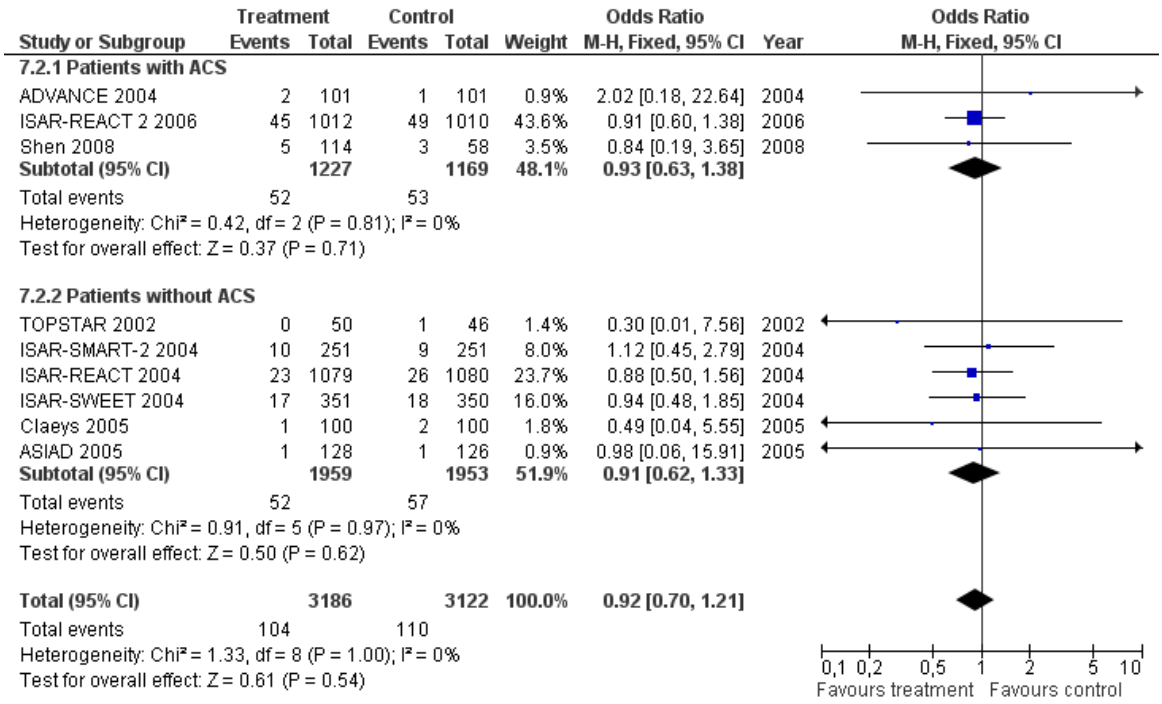
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

Total (95% CI)		**3809**		**3747**	**100.0%**	**0.83 [0.56, 1.22]**	
Total events	48		55				

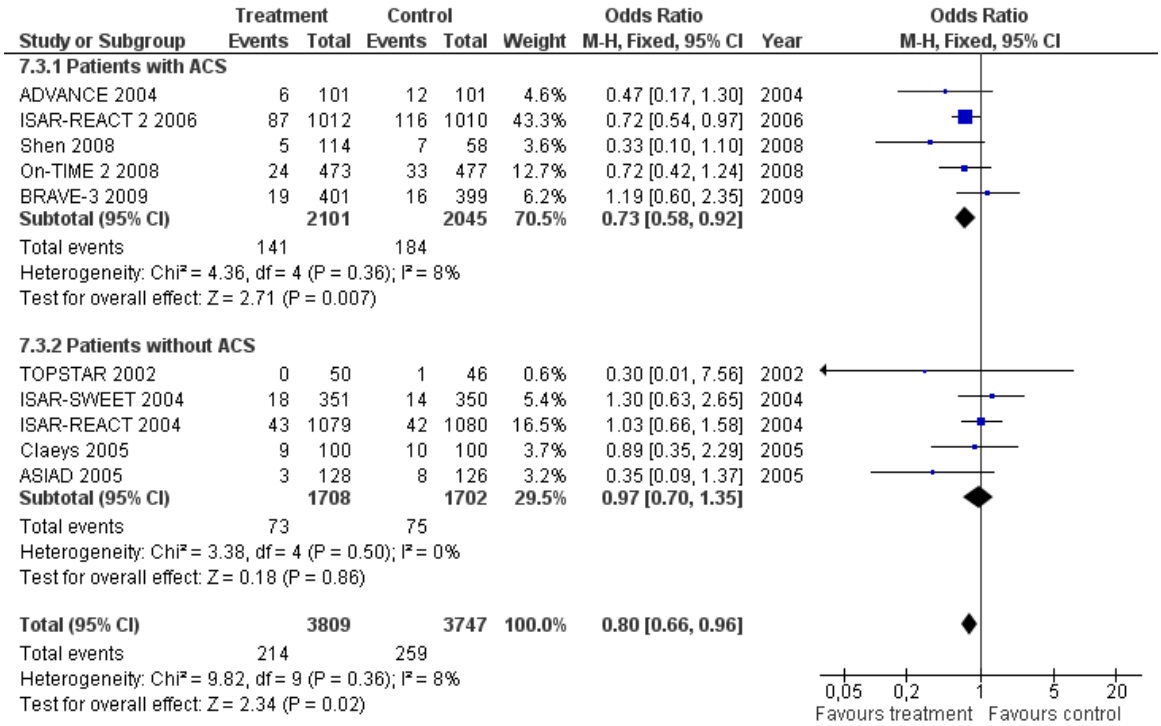
Heterogeneity: Chi² = 2.91, df = 6 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)



7.2 6-month mortality

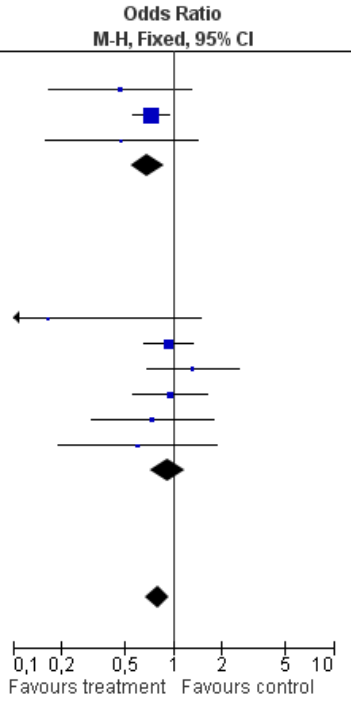


7.3 30-day mortality or myocardial infarction



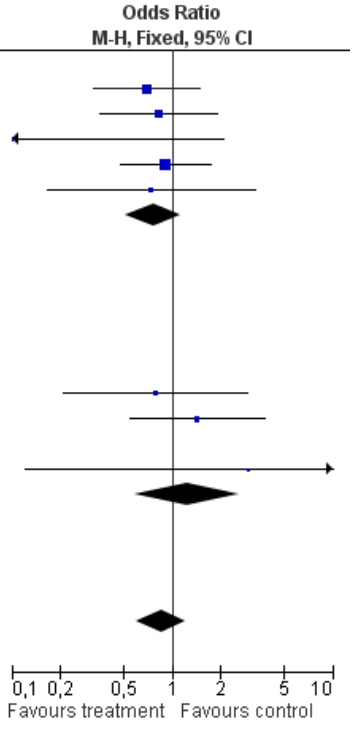
7.4 6-month mortality or myocardial infarction

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
7.4.1 Patients with ACS							
ADVANCE 2004	6	101	12	101	3.9%	0.47 [0.17, 1.30]	2004
ISAR-REACT 2 2006	117	1012	154	1010	47.2%	0.73 [0.56, 0.94]	2006
Shen 2008	7	114	7	58	3.0%	0.48 [0.16, 1.43]	2008
Subtotal (95% CI)		**1227**		**1169**	**54.1%**	**0.69 [0.54, 0.89]**	
Total events	130		173				
Heterogeneity: Chi² = 1.14, df = 2 (P = 0.57); I² = 0%							
Test for overall effect: Z = 2.94 (P = 0.003)							
7.4.2 Patients without ACS							
TOPSTAR 2002	1	50	5	46	1.8%	0.17 [0.02, 1.49]	2002
ISAR-REACT 2004	65	1079	69	1080	22.4%	0.94 [0.66, 1.33]	2004
ISAR-SMART-2 2004	22	251	17	251	5.4%	1.32 [0.68, 2.55]	2004
ISAR-SWEET 2004	29	351	30	350	9.5%	0.96 [0.56, 1.64]	2004
Claeys 2005	10	100	13	100	4.1%	0.74 [0.31, 1.78]	2005
ASIAD 2005	5	128	8	126	2.7%	0.60 [0.19, 1.89]	2005
Subtotal (95% CI)		**1959**		**1953**	**45.9%**	**0.92 [0.72, 1.18]**	
Total events	132		142				
Heterogeneity: Chi² = 4.30, df = 5 (P = 0.51); I² = 0%							
Test for overall effect: Z = 0.65 (P = 0.52)							
Total (95% CI)		**3186**		**3122**	**100.0%**	**0.80 [0.67, 0.95]**	
Total events	262		315				
Heterogeneity: Chi² = 8.18, df = 8 (P = 0.42); I² = 2%							
Test for overall effect: Z = 2.55 (P = 0.01)							



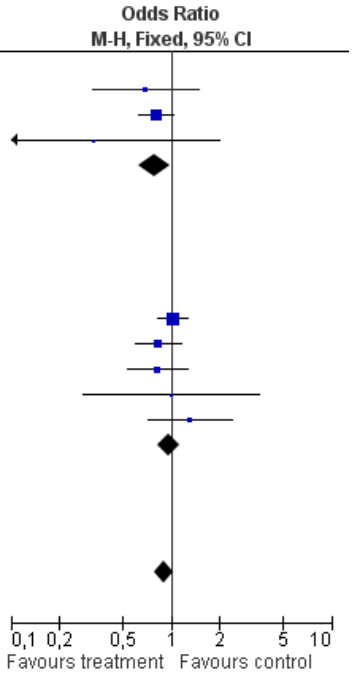
7.5 30-day urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
7.5.1 Patients with ACS							
ADVANCE 2004	14	101	19	101	24.4%	0.69 [0.33, 1.48]	2004
ISAR-REACT 2 2006	10	1012	12	1010	17.7%	0.83 [0.36, 1.93]	2006
Shen 2008	0	114	2	58	4.9%	0.10 [0.00, 2.09]	2008
On-TIME 2 2008	18	473	20	477	28.6%	0.90 [0.47, 1.73]	2008
BRAVE-3 2009	3	401	4	399	5.9%	0.74 [0.17, 3.35]	2009
Subtotal (95% CI)		**2101**		**2045**	**81.5%**	**0.77 [0.51, 1.14]**	
Total events	45		57				
Heterogeneity: Chi² = 2.08, df = 4 (P = 0.72); I² = 0%							
Test for overall effect: Z = 1.31 (P = 0.19)							
7.5.2 Patients without ACS							
TOPSTAR 2002	0	50	0	46		Not estimable	2002
ISAR-SWEET 2004	4	351	5	350	7.4%	0.80 [0.21, 2.99]	2004
ISAR-REACT 2004	10	1079	7	1080	10.3%	1.43 [0.54, 3.78]	2004
Claeys 2005	0	100	0	100		Not estimable	2005
ASIAD 2005	1	128	0	126	0.7%	2.98 [0.12, 73.76]	2005
Subtotal (95% CI)		**1708**		**1702**	**18.5%**	**1.24 [0.59, 2.62]**	
Total events	15		12				
Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² = 0%							
Test for overall effect: Z = 0.56 (P = 0.57)							
Total (95% CI)		**3809**		**3747**	**100.0%**	**0.85 [0.60, 1.21]**	
Total events	60		69				
Heterogeneity: Chi² = 3.96, df = 7 (P = 0.78); I² = 0%							
Test for overall effect: Z = 0.88 (P = 0.38)							



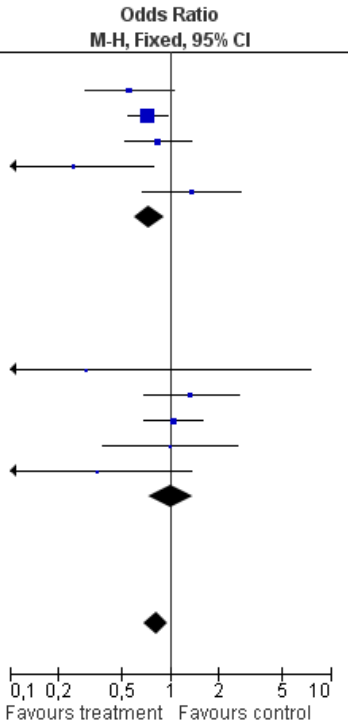
7.6 6-month urgent revascularisation

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
7.6.1 Patients with ACS							
ADVANCE 2004	14	101	19	101	3.5%	0.69 [0.33, 1.48]	2004
ISAR-REACT 2 2006	137	1012	164	1010	30.4%	0.81 [0.63, 1.03]	2006
Shen 2008	2	114	3	58	0.8%	0.33 [0.05, 2.02]	2008
Subtotal (95% CI)		**1227**		**1169**	**34.7%**	**0.78 [0.62, 0.99]**	
Total events	153		186				
Heterogeneity: Chi² = 1.04, df = 2 (P = 0.59); I² = 0%							
Test for overall effect: Z = 2.05 (P = 0.04)							
7.6.2 Patients without ACS							
ISAR-REACT 2004	208	1079	204	1080	35.2%	1.03 [0.83, 1.27]	2004
ISAR-SWEET 2004	84	351	96	350	15.6%	0.83 [0.59, 1.17]	2004
ISAR-SMART-2 2004	47	251	55	251	9.6%	0.82 [0.53, 1.27]	2004
Claeys 2005	5	100	5	100	1.0%	1.00 [0.28, 3.57]	2005
ASIAD 2005	29	128	23	126	3.8%	1.31 [0.71, 2.42]	2005
Subtotal (95% CI)		**1909**		**1907**	**65.3%**	**0.97 [0.82, 1.13]**	
Total events	373		383				
Heterogeneity: Chi² = 2.53, df = 4 (P = 0.64); I² = 0%							
Test for overall effect: Z = 0.43 (P = 0.67)							
Total (95% CI)		**3136**		**3076**	**100.0%**	**0.90 [0.79, 1.03]**	
Total events	526		569				
Heterogeneity: Chi² = 5.66, df = 7 (P = 0.58); I² = 0%							
Test for overall effect: Z = 1.52 (P = 0.13)							



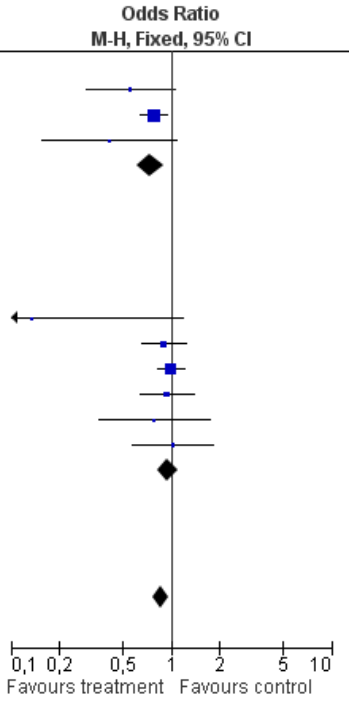
7.7 30-day mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
7.7.1 Patients with ACS							
ADVANCE 2004	20	101	31	101	9.3%	0.56 [0.29, 1.06]	2004
ISAR-REACT 2 2006	90	1012	120	1010	40.8%	0.72 [0.54, 0.97]	2006
On-TIME 2 2008	33	473	39	477	13.5%	0.84 [0.52, 1.36]	2008
Shen 2008	5	114	9	58	4.3%	0.25 [0.08, 0.78]	2008
BRAVE-3 2009	19	401	14	399	5.0%	1.37 [0.68, 2.77]	2009
Subtotal (95% CI)		**2101**		**2045**	**72.8%**	**0.74 [0.60, 0.92]**	
Total events	167		213				
Heterogeneity: Chi² = 7.42, df = 4 (P = 0.12); I² = 46%							
Test for overall effect: Z = 2.74 (P = 0.006)							
7.7.2 Patients without ACS							
TOPSTAR 2002	0	50	1	46	0.6%	0.30 [0.01, 7.56]	2002
ISAR-SWEET 2004	20	351	15	350	5.3%	1.35 [0.68, 2.68]	2004
ISAR-REACT 2004	45	1079	43	1080	15.4%	1.05 [0.68, 1.61]	2004
Claeys 2005	9	100	9	100	3.1%	1.00 [0.38, 2.63]	2005
ASIAD 2005	3	128	8	126	2.9%	0.35 [0.09, 1.37]	2005
Subtotal (95% CI)		**1708**		**1702**	**27.2%**	**1.01 [0.73, 1.40]**	
Total events	77		76				
Heterogeneity: Chi² = 3.57, df = 4 (P = 0.47); I² = 0%							
Test for overall effect: Z = 0.07 (P = 0.95)							
Total (95% CI)		**3809**		**3747**	**100.0%**	**0.81 [0.68, 0.97]**	
Total events	244		289				
Heterogeneity: Chi² = 13.60, df = 9 (P = 0.14); I² = 34%							
Test for overall effect: Z = 2.25 (P = 0.02)							



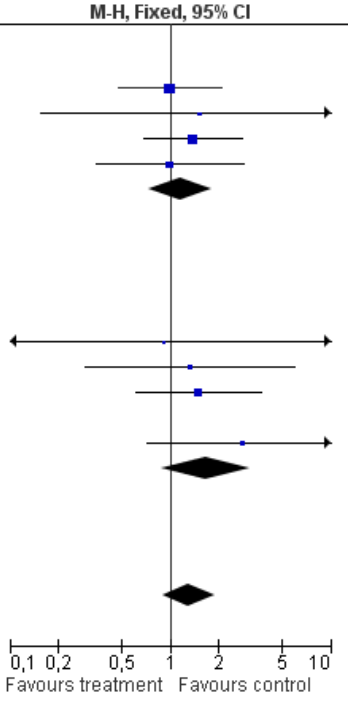
7.8 6-month mortality, myocardial infarction or urgent revascularisation

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
7.8.1 Patients with ACS							
ADVANCE 2004	20	101	31	101	4.0%	0.56 [0.29, 1.06]	2004
ISAR-REACT 2 2006	234	1012	281	1010	34.8%	0.78 [0.64, 0.95]	2006
Shen 2008	9	114	10	58	2.0%	0.41 [0.16, 1.08]	2008
Subtotal (95% CI)		**1227**		**1169**	**40.7%**	**0.74 [0.61, 0.89]**	
Total events	263		322				
Heterogeneity: Chi² = 2.43, df = 2 (P = 0.30); I² = 18%							
Test for overall effect: Z = 3.13 (P = 0.002)							
7.8.2 Patients without ACS							
TOPSTAR 2002	1	50	6	46	1.0%	0.14 [0.02, 1.18]	2002
ISAR-SWEET 2004	105	351	112	350	12.6%	0.91 [0.66, 1.25]	2004
ISAR-REACT 2004	257	1079	257	1080	31.5%	1.00 [0.82, 1.22]	2004
ISAR-SMART-2 2004	69	251	72	251	8.4%	0.94 [0.64, 1.39]	2004
Claeys 2005	13	100	16	100	2.2%	0.78 [0.36, 1.73]	2005
ASIAD 2005	29	128	28	126	3.5%	1.03 [0.57, 1.85]	2005
Subtotal (95% CI)		**1959**		**1953**	**59.3%**	**0.95 [0.82, 1.10]**	
Total events	474		491				
Heterogeneity: Chi² = 3.75, df = 5 (P = 0.59); I² = 0%							
Test for overall effect: Z = 0.66 (P = 0.51)							
Total (95% CI)		**3186**		**3122**	**100.0%**	**0.87 [0.77, 0.97]**	
Total events	737		813				
Heterogeneity: Chi² = 10.63, df = 8 (P = 0.22); I² = 25%							
Test for overall effect: Z = 2.45 (P = 0.01)							



7.9 30-day major bleeding

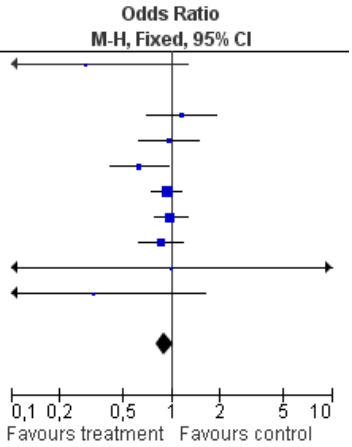
Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
7.9.1 Patients with ACS							
ADVANCE 2004	0	101	0	101		Not estimable	2004
ISAR-REACT 2 2006	14	1012	14	1010	27.6%	1.00 [0.47, 2.10]	2006
On-TIME 2 2008	3	114	1	58	2.6%	1.54 [0.16, 15.15]	2008
Shen 2008	19	473	14	477	26.7%	1.38 [0.69, 2.79]	2008
BRAVE-3 2009	7	401	7	399	13.8%	0.99 [0.35, 2.86]	2009
Subtotal (95% CI)		**2101**		**2045**	**70.7%**	**1.16 [0.74, 1.82]**	
Total events	43		36				
Heterogeneity: Chi² = 0.54, df = 3 (P = 0.91); I² = 0%							
Test for overall effect: Z = 0.66 (P = 0.51)							
7.9.2 Patients without ACS							
TOPSTAR 2002	1	50	1	46	2.0%	0.92 [0.06, 15.12]	2002
ISAR-SWEET 2004	4	351	3	350	5.9%	1.33 [0.30, 6.00]	2004
ISAR-REACT 2004	12	1079	8	1080	15.8%	1.51 [0.61, 3.70]	2004
ASIAD 2005	0	128	0	126		Not estimable	2005
Claeys 2005	8	100	3	100	5.5%	2.81 [0.72, 10.92]	2005
Subtotal (95% CI)		**1708**		**1702**	**29.3%**	**1.68 [0.88, 3.20]**	
Total events	25		15				
Heterogeneity: Chi² = 0.88, df = 3 (P = 0.83); I² = 0%							
Test for overall effect: Z = 1.57 (P = 0.12)							
Total (95% CI)		**3809**		**3747**	**100.0%**	**1.31 [0.91, 1.90]**	
Total events	68		51				
Heterogeneity: Chi² = 2.19, df = 7 (P = 0.95); I² = 0%							
Test for overall effect: Z = 1.45 (P = 0.15)							



8.1 30-day mortality

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
CANADIAN 1996	3	242	5	123	1.3%	0.30 [0.07, 1.26]	1996
Schulman 1996	0	153	0	74		Not estimable	1996
PARAGON A 1998	51	1524	22	758	5.5%	1.16 [0.70, 1.92]	1998
PRISM Plus 1998	49	1118	36	797	7.7%	0.97 [0.62, 1.50]	1998
PRISM 1998	37	1616	58	1616	10.9%	0.63 [0.41, 0.96]	1998
PURSUIT 1998	165	4722	175	4739	32.4%	0.94 [0.76, 1.17]	1998
GUSTO-IV 2001	199	5102	102	2598	25.0%	0.99 [0.78, 1.27]	2001
PARAGON B 2002	75	2600	85	2569	16.0%	0.87 [0.63, 1.19]	2001
ELISA-2 2006	1	162	1	163	0.2%	1.01 [0.06, 16.23]	2006
PRACTICE 2007	2	196	6	197	1.1%	0.33 [0.07, 1.65]	2007
Total (95% CI)		**17435**		**13634**	**100.0%**	**0.91 [0.80, 1.03]**	
Total events	582		490				

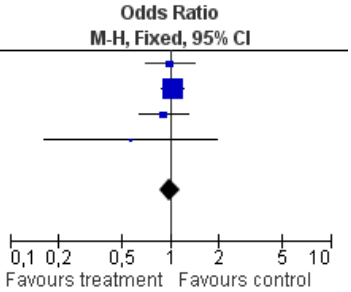
Heterogeneity: Chi² = 8.47, df = 8 (P = 0.39); I² = 6%
Test for overall effect: Z = 1.51 (P = 0.13)



8.2 6-month mortality

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
PRISM Plus 1998	78	1118	56	797	15.0%	0.99 [0.70, 1.42]
PURSUIT 1998	302	4722	294	4739	67.8%	1.03 [0.88, 1.22]
PARAGON A 1998	92	1524	50	758	15.5%	0.91 [0.64, 1.30]
PRACTICE 2007	4	196	7	197	1.7%	0.57 [0.16, 1.96]
Total (95% CI)		**7560**		**6491**	**100.0%**	**1.00 [0.87, 1.15]**
Total events	476		407			

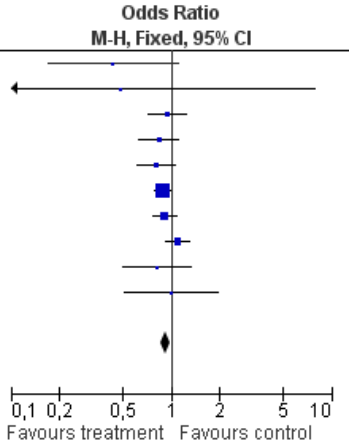
Heterogeneity: Chi² = 1.23, df = 3 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)



8.3 30-day mortality or myocardial infarction

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
CANADIAN 1996	9	242	10	123	0.8%	0.44 [0.17, 1.10]	1996
Schulman 1996	1	153	1	74	0.1%	0.48 [0.03, 7.79]	1996
PARAGON A 1998	171	1524	89	758	6.9%	0.95 [0.72, 1.25]	1998
PRISM Plus 1998	114	1118	95	797	6.5%	0.84 [0.63, 1.12]	1998
PRISM 1998	94	1616	115	1616	7.0%	0.81 [0.61, 1.07]	1998
PURSUIT 1998	670	4722	744	4739	41.5%	0.89 [0.79, 0.99]	1998
PARAGON B 2002	276	2600	295	2569	17.3%	0.92 [0.77, 1.09]	2001
GUSTO-IV 2001	450	5102	209	2598	16.4%	1.11 [0.93, 1.31]	2001
ELISA-2 2006	43	162	50	163	2.4%	0.82 [0.50, 1.32]	2006
PRACTICE 2007	19	196	19	197	1.1%	1.01 [0.52, 1.96]	2007
Total (95% CI)		**17435**		**13634**	**100.0%**	**0.92 [0.86, 0.99]**	
Total events	1847		1627				

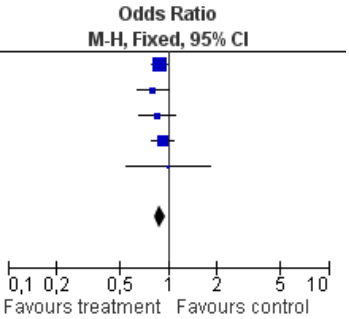
Heterogeneity: Chi² = 9.09, df = 9 (P = 0.43); I² = 1%
Test for overall effect: Z = 2.29 (P = 0.02)



8.4 6-month mortality or myocardial infarction

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
PURSUIT 1998	576	4722	644	4739	46.7%	0.88 [0.78, 1.00]	1998
PARAGON A 1998	229	1524	136	758	12.8%	0.81 [0.64, 1.02]	1998
PRISM Plus 1998	150	1118	122	797	10.2%	0.86 [0.66, 1.11]	1998
PARAGON B 2002	378	2628	400	2597	28.5%	0.92 [0.79, 1.07]	2001
PRACTICE 2007	24	196	24	197	1.7%	1.01 [0.55, 1.84]	2007
Total (95% CI)		**10188**		**9088**	**100.0%**	**0.88 [0.81, 0.96]**	
Total events	1357		1326				

Heterogeneity: Chi² = 1.10, df = 4 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.93 (P = 0.003)



8.5 30-day major bleeding

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Schulman 1996	6	153	1	74	0.3%	2.98 [0.35, 25.21]	1996
CANADIAN 1996	7	242	1	123	0.3%	3.63 [0.44, 29.87]	1996
PRISM 1998	6	1616	6	1616	1.3%	1.00 [0.32, 3.11]	1998
PARAGON A 1998	19	1524	6	758	1.7%	1.58 [0.63, 3.98]	1998
PRISM Plus 1998	11	773	6	797	1.3%	1.90 [0.70, 5.17]	1998
PURSUIT 1998	496	4679	427	4696	83.7%	1.19 [1.03, 1.36]	1998
PARAGON B 2002	34	2600	23	2569	5.0%	1.47 [0.86, 2.50]	2001
GUSTO-IV 2001	42	5102	7	2598	2.0%	3.07 [1.38, 6.85]	2001
ELISA-2 2006	20	162	16	163	3.1%	1.29 [0.64, 2.60]	2006
PRACTICE 2007	8	196	6	197	1.3%	1.35 [0.46, 3.98]	2007
Total (95% CI)		**17047**		**13591**	**100.0%**	**1.27 [1.12, 1.43]**	
Total events	649		499				

Heterogeneity: Chi² = 8.53, df = 9 (P = 0.48); I² = 0%

Test for overall effect: Z = 3.80 (P = 0.0001)