Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era (Review)

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[Intervention Review]

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ABSTRACT

Background

In patients with unstable angina and non-ST elevation myocardial infarction (UA/NSTEMI) two strategies are possible, either a routine invasive strategy where all patients undergo coronary angiography shortly after admission and, if indicated, coronary revascularization; or a conservative strategy where medical therapy alone is used initially, with selection of patients for angiography based on clinical symptoms or investigational evidence of persistent myocardial ischemia.

Objectives

To determine the benefits of an invasive compared to conservative strategy for treating UA/NSTEMI in the stent era.

Search methods

The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, Issue 1), MEDLINE and EMBASE were searched (1996 to February 2008) with no language restrictions.

Selection criteria

Included studies were prospective trials comparing invasive with conservative strategies in UA/NSTEMI.

Data collection and analysis

We identified five studies (7818 participants). Using intention-to-treat analysis with random-effects models, summary estimates of relative risk (RR) with 95% confidence interval (CI) were determined for primary end-points of all-cause death, fatal and non-fatal myocardial infarction, all-cause death or non-fatal myocardial infarction, and refractory angina. Further analysis of included studies was undertaken based on whether glycoprotein IIb/IIIa receptor antagonists were used routinely. Heterogeneity was assessed using Chi ^{2} and variance (I^2 statistic) methods.

Main results

In the all-study analysis, mortality during initial hospitalization showed a trend to hazard with an invasive strategy (RR 1.59, 95% CI 0.96 to 2.64). The invasive strategy did not reduce death on longer-term follow up. Myocardial infarction rates assessed at 6 to 12 months (5 trials) and 3 to 5 years (3 trials) were significantly decreased by an invasive strategy (RR 0.73, 95% CI 0.62 to 0.86; and RR 0.78, 95% CI 0.67 to 0.92 respectively). The incidence of early (< 4 month) and intermediate (6 to 12 month) refractory angina were both significantly decreased by an invasive strategy (RR 0.47, 95% CI 0.32 to 0.68; and RR 0.67, 95% CI 0.55 to 0.83 respectively), as were early and intermediate rehospitalization rates (RR 0.60, 95% CI 0.41to 0.88; and RR 0.67, 95% CI 0.61 to 0.74 respectively). The invasive strategy was associated with a two-fold increase in the RR of peri-procedural myocardial infarction (as variably defined) and a 1.7-fold increase in the RR of (minor) bleeding with no hazard of stroke.

Authors' conclusions

Compared to a conservative strategy for UA/NSTEMI, an invasive strategy is associated with reduced rates of refractory angina and rehospitalization in the shorter term and myocardial infarction in the longer term. However, the invasive strategy is associated with a doubled risk of procedure-related heart attack and increased risk of bleeding and procedural biomarker leaks. Available data suggest that an invasive strategy may be particularly useful in those at high risk for recurrent events.

PLAIN LANGUAGE SUMMARY

Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Patients with prolonged or recurrent chest pain may have a condition called unstable angina or suffer a certain type of heart attack called non-ST elevation myocardial infarction. These conditions can be managed with two main treatment strategies. Several studies have been done to determine which strategy is superior. In one strategy, the routine invasive strategy, all patients have a catheter inserted to image their coronary arteries and look for atherosclerotic narrowing. If a significant narrowing or complicated plaque is found then the artery may be dilated by means of a balloon catheter that is inserted and inflated across the narrowing. The patency of the vessel is maintained by insertion of a metallic stent. In some cases, the narrowing will not be amenable to this approach and surgery to bypass the narrowing is required. In the other conservative strategy, patients are initially treated with drugs and only those who suffer more chest pain while receiving the drugs or who demonstrate evidence of atherosclerotic narrowing as suggested by other non-invasive tests, such as stress testing or imaging, undergo coronary angiography and revascularization if indicated.

There has been debate as to which strategy is better. The invasive strategy reduces the incidence of further chest pain or rehospitalization. Also, long-term follow up from three studies suggests that it reduces the risk of having a heart attack in the three to five years following the event by 22%. However, the invasive strategy is associated with a doubled risk of procedure-related heart attack and increased risk of bleeding. Hence, available studies suggest that the invasive strategy may have particular benefit in patients who are at higher risk for recurrent events and that patients at low risk for a recurrent event may not derive benefit from invasive intervention. The level of risk that warrants intervention requires considerable further research.

BACKGROUND

The diagnosis of acute coronary syndromes

The acute coronary syndrome (ACS) encompasses three disorders of related etiology. These are ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA). The management of STEMI differs from that for UA and NSTEMI, which may be considered as one clinical entity (UA/NSTEMI). The pathogenesis of UA/NSTEMI involves five non-exclusive causative factors of non-occlusive thrombus on pre-existing plaque, dynamic obstruction, progressive mechanical obstruction, inflammation, and secondary unstable angina associated with increased cardiac work load (Braunwald 1998). Of these factors, thrombus formation on pre-existing plaque, that is acute plaque change, is the most common.

Indeed, the majority of patients with ACS have an acute change in coronary atherosclerotic plaques, with STEMI usually associated with complete occlusion of the involved vessel(s) (DeWood 1980) and UA/NSTEMI usually associated with subtotal occlusion (DeWood 1986; TIMI-IIIA 1993). The distinction between UA and NSTEMI depends on the presence of myocardial infarction as determined by markers of myocardial damage such as troponin I (TnI), troponin T (TnT) or creatine kinase (CK-MB). Compared to STEMI, NSTEMI has a lower 30-day mortality rate but more recurrent ischemia and a similar one-year mortality rate (Armstrong 1998). UA/NSTEMI is much more common than STEMI; in the United States, 1.4 million patients per year are admitted to hospital with ACS, approximately 70% with UA/NSTEMI (Rosamond 2008). Whereas emergency percutaneous coronary revascularization is now a commonly used therapy for treating STEMI (Antman 2004; Cucherat 2003), the role of angiography and possible subsequent revascularization is less clear in UA/NSTEMI. In overview, treatment of UA/NSTEMI initially involves medical therapy followed by one of two management strategies involving different rates of angiography and revascularization. The medical therapies for UA/NSTEMI are briefly reviewed before the focus of this review shifts to the management strategies of patients with UA/NSTEMI.

Initial medical management of UA/NSTEMI

In brief, medical treatments as outlined in the American College of Cardiologists (ACC) and American Heart Association (AHA) guidelines (Anderson 2007) fall into the two major groups of anti-ischemic therapies and anti-platelet or anti-coagulation therapies. Anti-ischemic therapies include bed rest, nitroglycerin, beta blocker (or non-dihydropyridine calcium antagonist if beta blockers are contraindicated) and an ACE inhibitor. Anti-platelet or anti-coagulation therapies include aspirin, clopidogrel, heparin and glycoprotein IIb/IIIa receptor antagonists. Randomized trial evidence to support use of most of these specific therapies has been published. Of anti-ischemic treatments, beta blockers have proven efficacy in patients with evolving myocardial infarction (Hjalmarson 1982; Yusuf 1988) as well as in patients with UA/NSTEMI (Gottlieb 1986; Muller 1984; Theroux 1985). Non-dihydropyridine calcium channel antagonists have proven efficacy in ACS (Boden 1991; Gibson 1986; Pepine 1998; Tijssen 1987) and are particularly useful in patients with contraindications to beta blockers. Both the early and late administration of angiotensin converting enzyme (ACE) inhibitors have been shown to be beneficial in myocardial infarction (EUROPA 2003; HOPE 2000; Rodrigues 2003). Of the anti-platelet or anti-coagulation treatments, aspirin has a consistent benefit in UA/NSTEMI as demonstrated in several clinical trials (Cairns 1985; Lewis 1983; RISC 1990; Theroux 1988). Likewise, clopidogrel has been shown to be beneficial in addition to aspirin (CURE 2001). Heparin, in its various forms, or fondaparinux have also been shown to be beneficial in UA/NSTEMI (Gurfinkel 1995; Mehta 2008; Neri Serneri 1990; RISC 1990; Theroux 1993). The glycoprotein IIb/IIIa receptor antagonists have proven efficacy in medical treatment of UA/NSTEMI (Boersma 2002; PRISM-PLUS 1998; PURSUIT 1998; Roffi 2002; Topol 1999) with the exception of abciximab (Simoons 2001). However, this class of drugs appears to have differential effects depending on the patients' risk level, with high-risk patients obtaining the most benefit. The glycoprotein IIb/IIIa receptor antagonists warrant special mention with regard to their use in invasive procedures. This concept is expanded on later.

Management following initial medical treatment: what is the role of early coronary angiography and revascularization?

Two different treatment strategies may be followed after initial medical treatment of UA/NSTEMI, an early invasive strategy of coronary angiography and, if indicated, revascularization in most or all patients who have no contraindication to such an approach; or a conservative ('ischemia guided') strategy in which patients undergo coronary angiography and revascularization only if there is evidence of recurrent ischemia. Examples are recurrent infarction, angina at rest, dynamic ST changes on electrocardiograph (ECG) or definitive inducible ischemia on provocative testing. Proponents of the early invasive strategy argue that the early determination of coronary anatomy can be used to tailor therapy, avoid lengthy hospital stays and prevent further events. For example, patients with normal coronary anatomy and minimal lumenal disease may be discharged. Those with coronary disease evident on angiography can be treated expeditiously according to their angiographic findings, which may include revascularization via percutaneous coronary intervention (PCI) comprising coronary angioplasty with or without insertion of coronary stent, or coronary artery bypass grafting (CABG). Proponents of the conservative strategy argue that medical therapy can stabilize patients. Stress testing can identify patients at risk of future events and who would therefore benefit most from invasive intervention, and the costs and complications of invasive procedures can be minimized by using invasive strategies more selectively. The evidence for the relative benefits and harms of these two approaches is the subject of this review.

Interpretation of the evidence from trials: changes in contemporary clinical practice

In routine clinical practice, the outcomes of invasive coronary procedures vary depending on a number of factors such as clinical expertise (Singh 2000); volume of procedures undertaken (Magid 2000); and methods and protocols used, especially in regard to pharmacological and procedural co-interventions. Of particular importance in contemporary practice are the use of glycopro-

tein IIb/IIIa receptor antagonists (CAPTURE 1997; EPIC 1994; EPILOG 1997; EPISTENT 1998; Karvouni 2003) and coronary artery stents (Al Suwaidi 2004), both of which have been shown to improve outcomes and reduce complications when used with invasive procedures. A report from the TIMI study group highlighted the importance of adjunctive therapy in the invasive strategy (Sabatine 2004). The TIMI group undertook two trials, with identical enrolment criteria, investigating treatment strategies in UA/NSTEMI, TIMI-3b 1995 and TACTICS-TIMI 18 (2001). The two trials were nearly a decade apart and, compared to TIMI-3b 1995, the more recent TACTICS-TIMI 18 study used pre-procedural (upstream) glycoprotein IIb/IIIa receptor antagonists and stents as standard treatment. Importantly, after adjustment for baseline risk, an early invasive strategy tended to have more favorable results in TACTICS-TIMI 18 than in TIMI-3b 1995. Further, stents with glycoprotein IIb/IIIa receptor antagonists as adjuncts to PCI have been associated with lower mortality (7.3% versus 14.4% at 6 months) compared to PCI with neither of these adjuncts, in the real-world GRACE registry (Montelascot 2003). Also, a meta-regression analysis of trials comparing early invasive and conservative strategies in UA/NSTEMI identified aggressive anti-platelet therapy and stenting as the two most significant predictors of the benefit of an invasive strategy in US/NSTEMI (Biondi-Zoccai 2005).

Stenting is associated with fewer major adverse cardiovascular events and a reduced need for emergency cardiac surgery (Al Suwaidi 2004). Specifically, the reduction in target vessel revascularization associated with stenting is of particular relevance to trials with longer durations of follow up. More recently, in patients with UA/NSTEMI treated with an early invasive strategy, bivalirudin with 'bailout' glycoprotein IIb/IIIa receptor antagonists has been proposed to produce non-inferior outcomes on ischemia end-points compared to standard heparin with glycoprotein IIb/IIIa receptor antagonists (Stone 2006, Stone 2007). However, the substitution of bivalirudin for herapin with glycoprotein IIb/IIIa receptor antagonists probably should not be undertaken unless patients have been pre-treated with a thienopyridine prior to angiography (Stone 2006). If the result of the ACUITY trial (Stone 2006) is confirmed, and future trials examining treatment strategies in UA/NSTEMI are undertaken using bivalirudin, these studies might be compared with studies that routinely used IIb/IIIa receptor antagonists during PCI.

Rationale for this review

UA/NSTEMI is a common hospital presentation and carries a significant mortality and risk for recurrent ischemic events. This review evaluated the relative merits of these strategies. The findings of this review are relevant to patients, physicians and to healthcare systems.

OBJECTIVES

The objectives of this review were two fold, to determine the benefits and harms of:

(1) an early invasive strategy compared to a conservative strategy for the management of UA/NSTEMI in the stent era;

(2) an early invasive strategy with and without glycoprotein IIb/IIIa receptor antagonists versus a conservative strategy for the management of UA/NSTEMI in the stent era.

METHODS

Criteria for considering studies for this review

Types of studies

Only studies undertaken in the stent era were considered for inclusion. If non-stent studies were to be included, the analysis would under-estimate the benefits of an early invasive strategy on end-points such as recurrent angina and rehospitalization (for example due to chest pain). The studies were randomized controlled clinical trials comparing invasive and conservative strategies in patients with UA/NSTEMI where at least one of this review's outcomes was measured. Revascularization approaches in studies that were included consisted of PCI or CABG as required. Stents had to be used appropriately in patients undergoing revascularization via PCI. Studies that did not meet this criterion were not deemed relevant to current practice and were excluded. The effects on outcomes of use of glycoprotein IIb/IIIa receptor antagonists were investigated further by undertaking two separate analyses of trials that did and did not routinely use glycoprotein IIb/IIIa receptor antagonists during percutaneous revascularization.

Analysis 1: all studies that deployed stents routinely in revascularization procedures using PCI, regardless of glycoprotein IIb/IIIa receptor antagonist use;
Analysis 2: stents and glycoprotein IIb/IIIa receptor antagonists deployed routinely in revascularization procedures using PCI;
Analysis 3: stents but not glycoprotein IIb/IIIa receptor antagonists deployed routinely in revascularization procedures using PCI.

Types of participants

Included studies recruited men and women aged at least 18 years who had an episode of angina with an accelerating pattern of pain at rest. The episode of pain must have occurred within 72 hours of randomization. Further, the patients were required to have at least one of the following:
(1) new ST depression;

(2) transient (< 20 minute) ST elevation;
(3) ischemic T-wave inversion or T-wave inversion in at least two contiguous leads;
(4) elevated levels of cardiac markers i.e. troponins or creatine kinase (CK-MB);
(5) coronary artery disease, as determined by a history of catheterization, revascularization, or ACS.
Included studies excluded patients if they had any of the following:
(1) persistent ST elevation (i.e. > 20 minutes);
(2) secondary angina (e.g. due to anemia or thyrotoxicosis);
(3) serious systemic disease or major co-morbidities that would preclude an invasive approach;
(4) severe congestive heart failure or cardiogenic shock.

Types of interventions

All patients with UA/NSTEMI were initially treated with some or all of the medical therapies discussed in the background; these are summarized in Table 1. Following initial medical therapy, patients were randomized to either early invasive or conservative treatment. The two treatment strategies differed with regard to the use of angiography and subsequent revascularization rates.
The two management strategies that were compared were as follows.
(1) Routine invasive strategy: routine angiography with or without revascularization in all patients. This was carried out in all eligible patients unless they had contraindications to angiography.
(2) Conservative strategy: angiography with or without revascularization only in eligible patients with evidence of cardiac ischemia e.g. recurrent ischemia, dynamic ECG changes or a positive stress test.
Revascularization modalities included PCI or CABG, depending on angiographic findings. CABG is indicated in lieu of PCI when one of the following criteria are met:

- three vessel disease and an ejection fraction (EF) < 0.50;
- two vessel disease with proximal left anterior descending involvement and EF < 0.50 or ischemia;
- left main coronary artery disease.

Types of outcome measures

Primary outcomes

(1) Death: all causes
(2) Myocardial infarction (this end-point only included non-fatal myocardial infarction in the review protocol but the review includes fatal or non-fatal myocardial infarction)
(3) Death (all causes) or non-fatal myocardial infarction
(4) Refractory angina

Secondary outcomes

(1) Rehospitalization for acute coronary syndromes
(2) Complications of angiography or revascularization i.e. bleeding, procedure-related myocardial infarction or stroke
Differentiating peri-PCI enzyme leaks from the outcome measure of non-fatal myocardial infarction warrants further comment. A universal definition of myocardial infarction, including peri-procedural myocardial infarction, has been adopted only recently and defines peri-procedural myocardial infarction as a biomarker increase to three times the upper reference limit (Thygesen 2007). Unfortunately, as is summarized in Table 2, peri-procedural myocardial infarction was variably defined in the included studies and this limited the interpretation of data across trials. The TACTICS-TIMI 18 definition most closely matches the the current universal definition. Further, not all included studies involved the routine measurement of cardiac enzymes following PCI. This point is discussed further under the heading 'Outcomes'.

Search methods for identification of studies

The databases that were searched included: Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, Issue 1), MEDLINE (1996 to February 2008) and EMBASE (1996 to February 2008). No language restrictions were applied. The restriction of 1996 onwards was applied because of low rates of stent use prior to that year. See Appendix 1 for details of the search strategies.
Further, reference lists of retrieved articles were searched and experts in the field contacted for additional information.

Data collection and analysis

Selection of studies

Two review authors (MRH, JAD) independently selected articles for inclusion in the review. JAD was an author on a previous version of this review. A study was considered eligible for inclusion if it was a prospective trial that compared the routine invasive strategy with the conservative strategy in patients with UA/NSTEMI. Specific exclusion criteria are mentioned in the 'Types of studies' section above. Data for this update were extracted by MRH using double data entry.

Data extraction and management

Data were extracted independently by two review authors (MRH, JAD) onto data extraction sheets. Disagreement was resolved first by consensus and then by consultation with CNA and IAS.

Quality assessment

All included studies were assessed independently by two review authors for quality. Please refer to the table 'Characteristics of included studies' for quality assessment of the included studies. The criteria used were those recommended by the Cochrane Heart Group.

(1) Treatment assignment: was treatment assignment truly random?

(2) Blinding: were the patients and investigators unaware of the treatment assignment?

(3) Selection bias after treatment assignment: were all patients signed up for the trial accounted for at trial conclusion? Were the conclusions reached by intention-to-treat analysis?

Statistical considerations

Data were analysed on an intention-to-treat basis. Where appropriate, data from all trials were combined using the meta-analysis software in Review Manager. All the outcome measures of this review were dichotomous. Data were combined using random-effects modeling to determine a summary estimate of the relative risk (RR) and the 95% confidence interval (CI). Heterogeneity was statistically assessed using the Chi^2 test ($P < 0.10$) for all end-points and the I^2 statistic (Higgins 2003) for selected end-points. The I^2 statistic was displayed on the forest plots for all analyses. Further, sensitivity analysis was undertaken for various pre-specified variables that may present sources of interstudy heterogeneity. Since this meta-analysis contained a small number of included studies and we previously identified many potential sources of heterogeneity (Hoenig 2006), meta-regression was not undertaken. As such we felt that an individual patient data meta-analysis would be more appropriate (Thompson 2005). Further, it would avoid aggregation bias. Given the differing definitions of myocardial infarction between the studies (Table 2), mortality at end of follow up was used when assessing publication bias or heterogeneity via sensitivity analysis. As stated under the heading 'Types of studies', all included studies were further analysed by assignment to one of two analyses depending on the routine use of glycoprotein IIb/IIIa receptor antagonists. We compared the invasive strategy versus the conservative strategy within each analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

The literature search yielded 2221 hits. From these, 31 papers reporting on 14 studies were selected for closer attention. One study was excluded because it was based on a registry and hence contained observational data (MITI 2000). Another study was excluded because it was a post hoc analysis of a trial comparing hirudin to heparin in ACS patients (GUSTO2b 2003). Four trials were excluded because they were undertaken in the pre-stent era or did not encourage the routine use of stents in the invasive strategy (MATE 1998; TIMI-3b 1995; VANQWISH 1998; Zhao 2005). Further, some studies included patients with STEMI but did not report outcomes separately for UA/NSTEMI (Eisenberg 2005; MATE 1998;). As was already stated, studies from the pre-stent era under-estimate the value of the invasive strategy and are not relevant to current practice. Also, two studies were excluded because of inappropriate patient selection or trial design (Neumann 2003; TRUCS 2000). More details on excluded studies can be found in the Characteristics of excluded studies table. Five studies were deemed appropriate for inclusion and are described in the Characteristics of included studies table. These five studies were analysed together in Analysis 1. Two of the studies used a glycoprotein IIb/IIIa antagonist routinely in the invasive arm (ICTUS; TACTICS-TIMI 18). These two studies were analysed together in the pre-specified Analysis 2 (see Types of studies). The three remaining studies satisfied this review's stent requirement but did not routinely use glycoprotein IIb/IIIa antagonists in patients randomized to the invasive strategy. They were analysed together as Analysis 3 (FRISC-II; RITA-3; VINO). This section discusses some general design features of the included studies and comments on the specific differences between the studies.

Design

All studies were randomized controlled trials (RCTs). Due to the procedural nature of the intervention, it was presumed that the patients and treating clinicians were not blinded. However, outcomes were able to be assessed by a blinded committee. The table of included studies describes trial design features and includes information on intention-to treat-analysis and losses to follow up.

Populations

The included studies were heterogeneous in their patient selection criteria. The inclusion criteria were made up of different combinations of the following core criteria: chest pain, ECG changes, increased level of cardiac markers or documented history of coronary artery disease (CAD). The specific criteria for each study are outlined in the table of included studies. Clearly, since different criteria were used by different studies, different trials randomized patients with different levels of risk. Elevated troponins (Antman 1996; Galvani 1997; Lindahl 1996) or ECG changes (Cannon 1997) forebode worse prognosis in UA/NSTEMI and hence trials recruiting these patients could be expected to have higher event rates. The VINO study randomized patients who had chest pain, ECG changes and elevated cardiac markers; whereas in TACTIC-

TIMI 18, 27% of the trial participants had accelerating or prolonged chest pain with a history of CAD as the sole entry criteria. In contrast, the entry criteria of the RITA-3 study were explicitly aimed at intermediate risk patients. The most recent trial in the review (ICTUS) included patients with a positive troponin and either ischemic ECG changes or a documented history of CAD.

Interventions

In the invasive strategy, all patients were randomized to receive angiography regardless of symptomatic status. In contrast, in the conservative strategy, angiography was only performed in patients with clinical or investigational evidence of ischemia. It is important to note that angiography is a component of both strategies and that angiography in the conservative arm did not represent a 'cross over' as long as it was preceded by myocardial ischemia or evidence for CAD.

Time to interventions

Time to angiography after symptom onset may influence efficacy. The times to angiography after randomization in the routine invasive arms were: mean 6.2 hours in VINO, median 22 hours in TACTICS-TIMI 18, median 23 hours in ICTUS, median two days in RITA-3 and mean four days in FRISC-II. The FRISC-II investigators cited observational data to justify delayed angiography and postulated that a period of "plaque passivation" prior to angiography would be beneficial. However, Neumann 2003 subsequently compared an 'early invasive' (angiography within six hours of randomization) to 'delayed invasive' (angiography in three to five days) strategy in UA/NSTEMI patients and found that early angiography produced superior outcomes to delayed angiography. More recently, the TIMACS 2008 study group compared an 'early invasive' (angiography within 24 hours of randomization, median 14 hours) to 'delayed invasive' (angiography after 36 hours, median 50 hours) in UA/NSTEMI patients. The TIMACS 2008 study group showed no hazard for an early invasive strategy compared to a delayed invasive strategy and also showed that in high risk patients the early invasive strategy produced more favorable clinical outcomes. These findings need further confirmation but suggest that high risk patients, in particular, benefit from expedited intervention. Given that the trials in this review are more consistent with a 'delayed invasive' strategy, it is possible that the available data under-estimate the potential effectiveness of the invasive strategy.

Criteria for ischemia

There were important differences between trials in the criteria for ischemia that mandated angiography in the conservative arm. In particular, the FRISC-II criteria were widely criticized for being more stringent than those of the other studies, thereby exaggerating benefit conferred by the invasive strategy. Further, FRISC-II did not utilize nuclear imaging or pharmacologic stress testing in the conservative strategy. Indeed, application of the FRISC-II criteria to the VANQWISH study, which recruited similar patients, suggests that significant CAD was under-detected in the conservative arm of the FRISC-II study (Goyal 2002).

Outcomes

Commonly reported outcomes included death, myocardial infarction and recurrent angina. Death was reported as all-cause death. The definition of myocardial infarction varied between the included studies but included a combination of chest pain, ECG changes and elevated cardiac enzymes. Peri-PCI enzyme leaks without other criteria were not reported as an end-point by all studies but were included as a safety outcome where data were available. The variable definitions of myocardial infarction are summarized in Table 2 and show that some of the studies required clinical or ECG, or both, changes for the myocardial infarction end-points whereas others only required an increased cardiac marker. Importantly, the ICTUS trial protocol mandated the routine measurement of CK-MB after PCI and this constituted the end-point of myocardial infarction. The significance of peri-PCI enzyme leaks is a subject of considerable debate (Bhatt 2005; Cutlip 2005). The other trials in this review did not specify the routine measurement of CK-MB after PCI per protocol. Fortunately the ICTUS investigators reported 'spontaneous' and 'peri-procedural' myocardial infarction as separate end-points (de Winter 2005; Hirsch 2007; Windhausen 2007b). Extracting data from ICTUS, which combined spontaneous and procedural myocardial infarction into a single myocardial infarction end-point, caused significant heterogeniety in a previous version of this meta-analysis (Hoenig 2006). Hence, to maximize consistency between trials, in our analysis we analysed 'spontaneous' myocardial infarction from the ICTUS trial with our myocardial infarction end-point and reported peri-procedural myocardial infarction as a safety end-point. This not only minimized heterogeniety in meta-analysis but is also justifiable since the significance of peri-procedural biomarker leaks is still a subject of contention. Fortunately, end-points such as death are indisputable. Follow up was six months in TACTICS-TIMI 18 and VINO, three years for myocardial infarction but four years for mortality in ICTUS, five years in FRISC-II and five years in RITA-3. Characteristics of the included studies are summarized in the table 'Characteristics of included studies' and in Table 1.

Risk of bias in included studies

The methodological quality of the included studies is summarized in the table 'Characteristics of included studies'.

Effects of interventions

The baseline patient characteristics were equivalent between the two randomized groups of all the included studies. TACTICS-TIMI 18 and ICTUS were analysed together in Analysis 2 since they involved the routine use of both glycoprotein IIb/IIIa receptor antagonists and stents. Analysis 3 included studies that used only stenting routinely and included RITA-3, FRISC-II and VINO. Since the included studies reported outcomes after different durations of follow up, end-points for meta-analysis were categorized as being index, early, intermediate or late. 'Index' end-points indicate follow up during the initial hospitalization. 'Early' end-points indicate a follow up less than or equal to four months. 'Intermediate' end-points indicate a follow up greater than or equal to six months, or less than or equal to 12 months. 'Late' end-points indicate a follow up greater than or equal to two years. In studies that supplied end-points at various time points in a given category, the latest follow up outcomes were used. For example, if outcomes were provided at six and 12 months follow up, the 12-month data were used in the analysis.

Analysis 1: all studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor antagonist use (TACTICS-TIMI 18, ICTUS, RITA-3, FRISC-II, VINO)

Death (index, early, intermediate, late)

Index death showed a trend to hazard with the early invasive strategy, having a RR of 1.53 (95% CI 0.98 to 2.39). Early and intermediate death were not improved by an invasive strategy and neither was late death, which included data from FRISC-II (5 years), RITA-3 (5 years) and ICTUS (4 years) (RR 0.90, 95% CI 0.76 to 1.08). Significant heterogeneity (P = 0.09) was detected in the analysis of intermediate death, which was the only analysis that included data from all five included studies. The I^2 statistic for the intermediate death analysis was 51% which indicated that the finding of heterogeneity cannot be assumed to be due to chance. Some of the heterogeneity at the intermediate (six to 12-month) time point may be explained by differences between trials in death rates standardized to years of study duration, shown in Table 1. The rates were 1.9% to 2.8% per year for RITA-3, FRISC-II and ICTUS; whereas TACTICS-TIMI 18 had a rate of 7% and VINO a rate of 27%. For the most part, the levels of risk were concordant with the inclusion criteria of the studies, as described in the table of included studies. with the exception of ICTUS. As already discussed, mortality increases as troponin concentrations increase in patients with ACS (Antman 1996). The ICTUS trial exclusively enrolled patients with a TnT > 0.03 ng/ml and hence may be expected to have a higher mortality rate. Indeed, in TACTICS-TIMI 18 the six-month mortality rate for patients with a TnT > 0.01 ng/ml was 4% (Morrow 2001). Since the ICTUS trial recruited patients with TnT > 0.03 ng/ml and had a longer duration of 12-months, the standardized mortality would be expected to be > 4%. Indeed, in FRISC-II patients with TnT > 0.03 ng/ml had a 12-month mortality rate of 4.2% (Diderholm 2002). Hence the ICTUS participants appear to have a lower than expected event rate based on event rates from other trials. Differences between trials in baseline medical therapy do not appear to explain why participants in the ICTUS trial had a lower mortality than other trials, particularly when comparing high rates of background medical therapy seen in both ICTUS and TACTICS-TIMI 18. This observation highlights the importance of global risk stratification over the selection of a single high risk characteristic in predicting risk of future events.

Long term (two to five-year) follow up can be seen by the mortality rates at end of follow up, described in Table 1. The studies with the highest mortality at end of follow up were those that randomized the highest risk patients (VINO) and those that had the longest follow up (for example RITA-3 compared to TACTICS-TIMI 18). It may be inappropriate to simply consider outcomes at one time point, for example at end of follow up as meta-analyses of this topic have done (Choudhry 2005; Mehta 2005), since it may be only on long term follow up that mortality curves diverge. Further, absolute risk reductions and numbers needed to treat (NNT) are meaningless from such analyses unless studies are homogenous for duration of follow up and risk level of participants. Clearly, long term studies or those enrolling higher risk participants will have a smaller NNT compared to those of shorter duration or involving lower risk patients. Further, long term follow up may be required to show a benefit for intervention since the mortality benefit of CABG over medical therapy for stable angina only emerges after three years and following an early hazard for surgery (Yusuf 1994). The aggregate number of patients followed up for late mortality was probably inadequate to make firm conclusions and this issue of sample size power is explored further in the discussion.

Myocardial infarction (index, early, intermediate, late)

Index myocardial infarction was not significantly affected by an invasive strategy, although significant heterogeneity was found at this time point (P < 0.01). Possible reasons for this finding include the use of glycoprotein IIb/IIIa receptor antagonists in TACTICS-TIMI 18 and the definition of myocardial infarction used by the VINO investigators, which excluded any events in the first 72 hours of randomization (Table 2). Early myocardial infarction was not significantly decreased by an early invasive strategy. Intermediate myocardial infarction included data from all the included studies as assessed at either six or 12 months. An early invasive strategy significantly reduced rates of myocardial infarction (RR 0.73, 95% CI 0.62 to 0.86). If the trial-preferred definition of myocardial infarction for ICTUS data was utilized instead (Table 2) there would have been no benefit for the early invasive strategy, with significant heterogeneity (P = 0.02, I^2 = 66%). In light of the controversy regarding peri-PCI enzyme leaks, we have ex-

tracted 'spontaneous' myocardial infarction from the ICTUS to allow comparability with other trials. Also, as mentioned previously, ICTUS was the only study that routinely measured biomarkers in all patients peri-procedurally. Late myocardial infarction based on FRISC-II (five years), RITA-3 (five years) and ICTUS (three years) was similarly, significantly decreased by the invasive strategy (RR 0.78, 95% CI 0.67 to 0.92).

Death or non-fatal myocardial infarction (index, early, intermediate, late)

The ICTUS investigators did not report the end-point of death or (spontaneous) myocardial infacrtion at index one year but reported it at three years. Index death or non-fatal myocardial infarction was not decreased by an early invasive strategy; significant heterogeneity was found and possible reasons include those already discussed for components of the composite outcome. Early death or non-fatal myocardial infarction, based on 30-day TACTICS-TIMI 18 data and VINO data, was significantly decreased by an invasive strategy with a RR of 0.64 (95% CI 0.45 to 0.92). Intermediate death or non-fatal myocardial infarction was significantly decreased with an early invasive strategy and included data from all included studies except for ICTUS (RR 0.76, 95% CI 0.62 to 0.94). No significant heterogeneity was found. Late death or non-fatal myocardial infarction was not significantly decreased (RR 0.89, 95% CI 0.73 to 1.08). The late follow up for this composite end-point was perhaps less important given the indendent benefit observed for the myocardial infarction end-point at late follow up and the 'dilution' of this effect by the incorporation of mortality into a composite outcome.

Combining data for subgroup analysis was not possible because TACTICS-TIMI 18 dichotomized patients at TnT = 0.01 ng/ml and TnI = 0.1 ng/ml, whereas FRISC-II presented data based on TnT levels of 0.1 ng/ml or 0.3 ng/ml. Gender subanalysis for intermediate death or non-fatal myocardial infarction showed that the benefit of the invasive strategy only reached statistical significance in males (RR 0.68, 95% CI 0.57 to 0.81). Interestingly, the data for women showed significant heterogeneity between the three studies (P = 0.05). No such heterogeneity was noted in the male data. This might be driven by FRISC-II data where women in the conservative group had significantly better outcomes than men in the conservative group (RR 0.52, 95% CI 0.36 to 0.75). However, the CI in the female subgroup was wide and overlapped that of their male counterparts. This is likely due to the small number of females in the included studies. Late (five-year) follow up from the FRISC-II investigators also showed that the invasive strategy only significantly benefitted males (RR 0.70, 95% CI 0.59 to 0.86). These subgroup analyses need to be interpreted with caution and are further explored in the discussion.

Refractory angina (early, intermediate)

An invasive strategy decreased early refractory angina based on four-month data from RITA-3 (RR 0.47, 95% CI 0.32 to 0.68). Intermediate refractory angina was significantly decreased by an early invasive strategy with a RR of 0.67 (95% CI 0.55 to 0.83) although significant heterogeneity (P < 0.01) was found at this time point, driven by the results of ICTUS. The null effect on this end-point found in ICTUS was surprising given that this study recruited only troponin-positive participants. Indeed, a retrospective analysis of troponin-positive patients from TACTIC-TIMI 18 showed that 94% of troponin-positive patients had significant angiographic CAD, 79% of which were revascularized (PCI or CABG) at index hospitalization (Dokainish 2005). Hence the trial participants in ICTUS would be expected to have high rates of angiographic CAD and would be expected to show considerable symptomatic improvement with an invasive strategy. A possible explanation for this difference in outcomes is that 20% of patients enrolled in ICTUS had PCI or CABG prior to randomization, indicating good baseline control of symptomatic angina.

Rehospitalization (early, intermediate, late)

The invasive strategy was associated with an early RR of 0.60 (95% CI 0.41 to 0.88) and an intermediate RR of 0.67 (95% CI 0.61 to 0.74). Late follow up on rehospitalization was provided by ICTUS at three years and showed that this benefit did not persist at three years (RR 0.79 (95% CI 0.56 to 1.12). This attenuation of the early benefit was not surprising considering the narrowing in the difference in revascularization rates between the two strategies in ICTUS, from 36% at initial hospitalization to 23% at end of follow up.

Analysis 2: routine use of both stents and glycoprotein IIb/IIIa receptor antagonists (TACTICS-TIMI 18, ICTUS)

This analysis included trials that were as close as possible to an 'ideal' invasive strategy, that is a strategy that involved the routine use of both glycoprotein IIb/IIIa receptor antagonists and stents.

Death (index, early, intermediate, late)

There was no difference between the treatment strategies at any of the time points assessed. Data from TACTICS-TIMI 18 and ICTUS at hospitalization (for index death) and from TACTICS-TIMI 18 at 30 days (for early death) showed a trend toward increased index death and early death (at 30 days) in the invasive arm but this did not reach statistical significance. Intermediate death was not different between the treatment strategies when six-month data from TACTICS-TIMI 18 and 12-month data from ICTUS were combined. In TACTIC-TIMI 18, the risk of death was not reduced by an early invasive strategy even in higher risk patients with TnI levels > 0.1 ng/ml. Late follow up

from ICTUS (four years) showed no benefit of an early invasive strategy on the death end-point at late follow up.

Myocardial infarction (index, early, intermediate, late)

Based on TACTICS-TIMI 18 and ICTUS data, the invasive strategy showed a trend toward a decrease in myocardial infarction during the Index hospitalization. Hence, there did not appear to be an early hazard to an invasive strategy when glycoprotein IIb/IIIa receptor antagonists were used upstream of PCI. Early myocardial infarction was reduced by an invasive strategy based on TACTICS-TIMI 18 data at 30 days (RR 0.53, 95% CI 0.35 to 0.79). Intermediate myocardial infarction was decreased by an invasive strategy using data for spontaneous myocardial infarction from ICTUS and data from TACTICS-TIMI 18 (RR 0.73, 95% CI 0.55 to 0.98). This finding became insignificant and significant heterogeneity resulted if the preferred definition of myocardial infarction by the ICTUS investigators was utilized (Table 2). As already discussed, the TACTICS-TIMI 18 investigators did not routinely measure CK-MB post-PCI (Table 2). Late follow up from ICTUS (three years) showed no benefit of an early invasive strategy on the rate of spontaneous myocardial infarction. In contrast to RITA-3 and FRISC-II, ICTUS was the only trial that included contemporary medical management (Table 1).

Death or myocardial infarction (index, early, intermediate, late)

Data for this end-point at index, early and intermediate time points were only available from TACTICS-TIMI 18. At index there was no difference between the treatment strategies. The invasive strategy was associated with an early (30-day) RR of 0.67 (95% CI 0.48 to 0.94). Baseline troponin levels were available from 1826 of 2220 trial participants and this data formed the basis for the pre-specified subgroup analysis based on TnT levels greater than (troponin positive) or less than (troponin negative) 0.01 ng/ml. Subgroup analysis showed that the early (30-day) benefit of the invasive strategy only reached statistical significance in troponin-positive patients (RR 0.50, 95% CI 0.32 to 0.79). Troponin-negative patients did not show significant benefit at 30-days follow up (RR 0.95, 95% CI 0.44 to 2.06) although this CI overlapped with those of troponin-positive patients. In contrast, at intermediate (six-month) follow up, the invasive strategy did not show any benefit regardless of baseline TnT status or gender. The results of this subgroup analysis changed when the TACTICS-TIMI 18 investigators used a different cardiac biomarker. With subgroup analysis based on a TnI cut-off of 0.1 ng/ml, troponin-positive patients showed early (30-day) and intermediate (six-month) benefits of an invasive strategy with RR of 0.47 (95% CI 0.30 to 0.73) and RR of 0.67 (95% CI 0.47 to 0.96) respectively. Such subgroup analysis based on troponin was pre-specified by the TACTICS-TIMI 18 investigators but should nevertheless be interpreted with caution. The ICTUS trial suggested no benefit of an early invasive strategy at late follow up regardless of baseline risk; this is explored further in the discussion.

Analysis 3: routine stent use but no routine glycoprotein IIb/IIIa receptor antagonist use (RITA-3, FRISC-II, VINO)

Death (index, early, intermediate, late)

There was a non-significant trend to increased death at index hospitalization and no effect on early death in the invasive strategy group. Intermediate death at six to 12 months was not significantly improved by an invasive strategy and significant heterogeneity was noted (P = 0.02). This may have been driven by the stringent criteria set by the FRISC-II group to define failure of conservative therapy; and by the large benefit of an invasive strategy observed in the small VINO study, which randomized patients with the highest death rates of all the included studies (Table 1). The FRISC-II investigators undertook subgroup analysis based on the presence of TnT greater than or less than 0.03 ng/ml and the presence of ST depression on the admission ECG. Mortality assessed at one year was not affected by an invasive strategy in this retrospective analysis, even in the group of patients with both TnT > 0.03 ng/ml and ST depression, although the numbers of patients may be too small to detect a difference. Follow up for late death was only provided by FRISC-II and RITA-3 at five years and was not significantly improved by an invasive strategy.

Myocardial infarction (index, early, intermediate, late)

There were no differences in index myocardial infarction rates between the two strategies although significant heterogeneity was found (P = 0.07). The FRISC-II data show a significant hazard for this end-point in the early invasive group (RR 2.22, 95% CI 1.46 to 3.36). Importantly, the three studies in this analysis did not undertake routine enzyme measurements post-PCI, as the ICTUS trial did, and used clinical symptoms as a diagnostic criterion (Table 2). Significant heterogeneity may be due to the VINO definition of myocardial infarction which excluded events within 72 hours of randomization in calculating this end-point. A hazard of the invasive strategy at index hospitalization would be expected, especially as these trials did not employ routine glycoprotein IIb/IIIa receptor antagonist use with PCI. Early myocardial infarction, based on 30-day VINO data and four-month RITA-3 data, was not significantly altered by an early invasive strategy. Intermediate (six-month data from VINO and 12-month data from FRISC-II and RITA-3) and late myocardial infarction (five-year FRISC-II and RITA-3 data) were significantly decreased by the invasive strategy (RR 0.72, 95% CI 0.52 to 0.98; RR 0.75, 95% CI 0.63 to 0.90 respectively).

Death or myocardial Infarction (index, early, intermediate, late)

The invasive strategy was associated with a trend to increased death or non-fatal myocardial infarction at index hospitalization. Significant heterogeneity (P = 0.06) was found, with FRISC-II data showing a significant hazard of the invasive strategy (RR 2.07, 95% CI 1.42 to 3.03). This trend to hazard may be related to the absence of adjunct glycoprotein IIb/IIIa receptor antagonist use with PCI. Early death or non-fatal myocardial infarction based on VINO 30-day data did not show a significant benefit with the invasive strategy. Intermediate death or non-fatal myocardial infarction also did not show a significant benefit of an invasive strategy, although significant heterogeneity was found (P = 0.09) driven by results of the small VINO trial favoring the invasive strategy. Although the VINO trial was small, the participants of this trial had the highest mortality rates (Table 1) and hence it was possible that these patients had the most to gain from an invasive strategy. Late death or non-fatal myocardial infarction, based on five-year results from FRISC-II and RITA-3 showed a significant benefit of this composite outcome with the invasive strategy (RR 0.81, 95% CI 0.72 to 0.92).

The FRISC-II data showed that the benefit of the invasive strategy in the end-point of intermediate (six to 12-month) death or non-fatal myocardial infarction was only significant in patients with ST depression at entry. The RR for this end-point was 0.66 (95% CI 0.50 to 0.88) at six and 12 months for patients who had ST depression. There was no benefit from a routine invasive strategy in patients without ST depression although such retrospective subgroup analysis needs to be interpreted with caution. Further, the FRISC-II troponin subgroup analysis found that troponin-positive participants (TnT > 0.1 ng/ml) had a RR of 0.71 (95% CI 0.53 to 0.93) at 12 months whereas participants with TnT < 0.1 ng/ml had only a trend for benefit with a RR of 0.77 (95% CI 0.53 to 1.11). Again, the CIs of these subgroup analyses overlap and the results should be regarded with caution. In a separate report, the FRISC-II investigators undertook subgroup analysis based on the presence of TnT greater than or less than 0.03 ng/ml and the presence of ST depression on admission ECG. The intermediate (one-year) death or non-fatal myocardial infarction end-point was only decreased significantly in the group of patients with both TnT > 0.03 ng/ml and ST depression > 0.1 mV (RR 0.60, 95% CI 0.43 to 0.82). Likewise, the FRISC-II investigators stratified patients by FRISC score when reporting late (five-year) outcomes for this end-point. These findings are explored in the discussion.

Safety end-points

Procedure-related myocardial infarction

Data from FRISC-II, RITA-3 and ICTUS showed that the invasive strategy was associated with an increased risk of procedure-related myocardial infarction (RR 2.00, 95% confidence interval 1.53 to 2.61). No heterogeneity was found despite the different diagnostic criteria: routine measurement of CK-MB post-PCI in ICTUS; FRISC-II and RITA-3 included clinical or ECG criteria in the definition of this end-point (Table 2). As already discussed, the significance of peri-procedural cardiac biomarker leaks is the subject of considerable ongoing debate but can be modified by background medications, including use of glycoprotein IIb/IIIa receptor antagonists (Cutlip 2005). While patients subjected to an invasive strategy in these trials had increased procedure-related myocardial infarction, this did not translate into an increased long-term mortality.

Bleeding

The invasive strategy was associated with an increased risk of bleeding (RR 1.71, 95% CI 1.27 to 2.31). Bleeding definitions varied between protocols; however, the excess bleeding was consistently due to minor bleeding associated with arterial access and wound site bleeding. Bleeding occurred in approximately 8% of patients in the invasive arm compared to 5% of patients in the conservative arm. The ICTUS investigators reported major bleeding which was defined as: fatal bleeding, intracranial bleeding, need for transfusion, a decrease in hemoglobin by 4.8 g/dl or bleeding causing hemodynamic compromise. Major bleeding occurred in 3.1% and 1.7% (p = NS) of patients randomized to an invasive and conservative strategy respectively during the initial hospitalization period. On four-year follow up, mortality was 18·6% in the 29 patients with major bleeding during initial hospitalization compared with 7·5% in the 1171 patients without in-hospital major bleeding (RR 2.68, 95% CI 1.08 to 6.61). Further data from randomized controlled trials are required regarding the risk of major bleeding (which is frequently defined differently) with an invasive strategy since numerous studies in UA/NSTEMI have identified major bleeding as a harbinger of a poor prognosis.

Stroke

Data from ICTUS and TACTICS-TIMI 18 showed no hazard for stroke with an early invasive strategy.

Contrast reactions

Allergic reactions due to the contrast used in angiography were more common in the invasive strategy than the conservative strategy. Typically, 1% of patients assigned to an invasive strategy developed contrast allergy. The rate in the conservative strategy depended on the proportion that underwent subsequent angiography and this depended on the population risk level. Contrast-induced renal failure was not reported, however this outcome can be modified by the patient's baseline renal function, hydration status and sodium bicarbonate.

Sensitivity analysis

Changing the methods for analysis from random-effects modeling to a fixed-effect model altered the interpretation of the data. The early myocardial infarction end-point and the late death or non-fatal myocardial infarction in Analysis 1 showed a significant benefit with an invasive strategy. However, random-effects modeling was chosen for the final presentation of the results as it provides a more conservative estimate of effect size in the presence of a small number of included studies and variable risk levels of randomized participants. Table 1 highlights important differences between the included studies which guided the choice of sensitivity analysis based on exclusion of certain studies. Recurrent angina and rehospitalization are end-points that were not subjected to sensitivity analysis because relative risk (RR) estimates were the most consistent and robust findings of this meta-analysis and, in general, were not associated with significant heterogeneity. The myocardial infarction end-point was not subjected to sensitivity analysis because of the variable definitions used in the included studies and the small numbers of trials. Consequently, the analyses below relate to the mortality end-point only.

Time to angiography

As previously discussed, time to angiography in the invasive arm may influence outcomes. Indeed, Neumann et al showed that in patients with UANSTEMI, a 'delayed invasive' strategy with angiography three to five days post-randomization had a relative risk of death or non-fatal myocardial infarction which was roughly two fold that observed in patients with an 'early invasive' strategy where angiography was performed within six hours of randomization. The excess events in the late invasive arm occurred prior to angiography; this was observed despite background anti-thrombotic therapy which included aspirin, clopidogrel, tirofiban and heparin. Notably, this study randomized a high risk population with roughly two thirds of the participants having a positive troponin and ST depression on ECG (Neumann 2003). Times to angiography in the included trials are shown in the table of included studies and can be grouped as 'early invasive' strategy versus 'delayed invasive' strategy. ICTUS, TACTICS-TIMI 18 and VINO generally employed angiography within 24 hours of randomization whereas the delay in FRISC-II and RITA-3 was typically greater than two days. Sensitivity analysis based on this study categorization did not yield results different from the previously reported findings of this review.

Mortality rates In the conservative arm

The mortality rates of the included studies are described in Table 1 as the mortality rate in the conservative arm divided by the number of years of follow up. ICTUS, FRISC-II and RITA-3 had mortality rates 1.9% to 2.8% per year of follow up while TACTICS-TIMI 18 had a rate of 7% and VINO a rate of 27%. Hence, the data for ICTUS, FRISC-II and RITA-3 were analysed separately, as were data for TACTICS-TIMI 18 and VINO. When the high-mortality rate studies and low-mortality rate studies were analysed separately, the previously reported findings of the review were not altered.

Percentage of trial participants with a positive troponin

Findings on subgroup analysis suggested that a positive troponin may identify high risk patients who may show particular benefit with an early invasive strategy. While VINO and ICTUS only recruited participants with positive cardiac biomarkers, the percentage of biomarker-positive patients in FRISC-II, RITA-3 and TACTICS-TIMI 18 ranged between 50% and 75% (Table 1). The studies that only randomized biomarker-positive patients (VINO and ICTUS) were analysed separately and showed a null effect on intermediate mortality. When the studies that did not specify cardiac biomarker status as an inclusion criterion were analysed separately, there was a significant increase in index death in the invasive arm (RR 1.72, 95% CI 1.05 to 2.82). This finding highlights potential hazards of an early invasive strategy and the importance of risk stratification to select high risk patients who may have meaningful benefits that outweigh the harms.

CABG as a mode of revascularization in the invasive arm

Data from trials of coronary revascularization in patients with stable CAD suggest that CABG may be the preferred mode of revascularization in higher risk patients with multi-vessel disease (Rihal 2003) and reduce death over long term follow up (Yusuf 1994). This statement should be in the background. Rates of CABG as mode of revascularization in the invasive arms of the included studies are described in Table 1. ICTUS and TACTICS-TIMI 18 had rates of approximately 20% while RITA-3, FRISC-II and VINO had rates of approximately 40%. Performing a sensitivity analysis on the basis of high or low rates of CABG in the invasive arm used the same data as already used in Analysis 2 and Analysis 3 and hence the findings were identical to those already described.

Difference in revascularization rates between the treatment arms

The absolute percentage difference in revascularization rates between the invasive and conservative arms of each trial is described in Table 1. FRISC-II and VINO had higher absolute differences in revascularization rates (28% to 39%) compared to the other included trials (17% to 23%). When the former trials were pooled, a significant reduction in intermediate death was noted (RR 0.49, 95% CI 0.25 to 0.95). This suggests that as the difference in rates of revascularization between invasive and conservative arms narrows, the benefit of a routine invasive strategy may diminish.

DISCUSSION

Summary of findings

In the all-study combined analysis, index death (during initial hospitalization) showed a trend to hazard with an invasive strategy with a RR of 1.59 (95% CI 0.96 to 2.64). Early death (< four months), intermediate death (six to 12 months) and late death (four to five years) were not significantly improved with an invasive strategy. Significant heterogeneity was found in this analysis possibly driven by the different levels of risk, different rates of background medical therapies and different criteria for ischemia in the included studies. Index myocardial infarction was not significantly improved with an early invasive strategy; significant heterogeneity was found on combining the data.

Myocardial infarction data at index hospitalization from trials that routinely used glycoprotein IIb/IIIa receptor antagonists showed a trend to benefit of the early invasive strategy, with a relative risk ratio of 0.67 (95% CI 0.44 to 1.02). Early myocardial infarction rates tended to be reduced with an early invasive approach; intermediate and late myocardial infarction were significantly reduced with an early invasive strategy with RR of 0.73 (95% CI 0.62 to 0.86) and 0.78 (95% CI 0.67 to 0.92) respectively. The studies that reported the death or myocardial infarction end-point suggest that benefits of an early invasive strategy were significant only in trial participants with high risk characteristics, that is positive troponin or ST depression on admission ECG, although this was not observed in the most contemporary study. These markers of risk may have identified populations with higher event rates and hence enhanced power to detect a difference between the two strategies. The CIs between subgroups overlapped and these findings from post hoc analyses should be interpreted with appropriate caution.

Early and intermediate refractory angina were both significantly decreased with an early invasive strategy; early RR 0.47 (95% CI 0.32 to 0.68) and intermediate RR 0.67 (95% CI 0.55 to 0.83). Early and intermediate rehospitalization were both significantly decreased with an early invasive strategy; early RR 0.60 (95% CI 0.41 to 0.88) and intermediate RR 0.67 (95% CI 0.61 to 0.74). However, in the most recent trial, the difference in hospitalization was not sustained at three years and this is perhaps explained by the narrowing difference in revascularization rates between the two strategies over time. The loss of symptomatic benefit associated with early intervention is also lost over time in patients with stable coronary disease (COURAGE 2007).

With regard to safety end-points, the invasive strategy was associated with a two-fold increase in the RR of the variably defined procedural myocardial infarction end-point and a 1.7 fold increase in the RR of bleeding, but no increase in RR of stroke. The excess in bleeding was mainly due to wound site bleeding but was difficult to grade due to inter-trial differences in definition and reporting of data.

Discussion of findings on subgroup analysis

Troponin status of patients

Troponin status of the patients serves as an important tool for risk stratification. Of the included studies, only TACTICS-TIMI 18 had the pre-specified intention of testing the 'troponin hypothesis', that is to test whether benefit from an invasive strategy was limited to troponin-positive patients. Data for the death or non-fatal myocardial infarction end-point from TACTICS-TIMI 18 and FRISC-II suggest that only high risk patients with a positive troponin benefited from an early invasive strategy with respect to this end-point. However, the CI for this subgroup analysis showed overlap with that of troponin-negative patients. Data from VINO, which only enrolled patients with clinical symptoms, ECG changes and positive cardiac biomarkers, showed a significant 72% relative risk reduction in this end-point at six months. However, the ICTUS trial which also exclusively enrolled troponin-positive patients had an unexpectedly low baseline mortality rate when compared to other included studies (Table 1). This may be partly due to optimal medical therapy in the ICTUS trial compared to other trials wherein, in both arms, early use of clopidogrel and intensive lipid-lowering therapy was recommended to treating clinicians. Disparate event rates in patients with positive troponin highlights the importance of global risk stratification as opposed to using cardiac biomarkers as a single risk index. Indeed, in retrospective analysis of the FRISC-II data (Diderholm 2002), death or non-fatal myocardial infarction showed a significant 40% relative risk reduction only in patients with both TnT > 0.03 ng/ml and ST depression on the admission ECG. Hence, although ICTUS participants all had a TnT > 0.03 ng/ml, this sole criterion did not necessarily identify a risk level that may be benefited by an invasive strategy.

A retrospective analysis by the TACTICS-TIMI 18 investigators highlights the limitations of purely using a positive troponin to predict event rates. An analysis of the invasive arm showed that 6% of the patients who had a positive troponin test did not have significant angiographic CAD as defined by a > 50% stenosis of any coronary artery (Dokainish 2005). At six months, these patients had a 3.1% rate of death or re-infarction compared to 0% for those with a negative troponin and no angiographic CAD. As would be expected, troponin-positive patients with angiographic CAD had a high 8.6% rate of death or re-infarction at six months. Interestingly, patients with angiographic CAD who had a negative troponin had a 5.8% rate of death or re-infarction at six months, which is clearly higher than that for troponin-positive patients without angiographic CAD. Hence, troponin alone cannot be used to risk stratify patients and this analysis highlights the limitations of angiography in the assessment of plaque burden. In general, in unstable angina studies a positive troponin status has been shown to correlate with complex coronary lesions on angiography and reduced coronary flow (Benamer 1999; Heeschen

1999a; Hochman 1999) but should not be used alone to identify a high risk population. However, absolute values of troponin show a linear relation with subsequent risk of coronary events; troponin positivity has also been shown to predict benefit from glycoprotein IIb/IIIa receptor antagonists (Hamm 1999; Heeschen 1999b) and remains a critical element of risk stratification.

ST depression on admission

As previously mentioned, ECG changes on admission forebode a worse prognosis in UA/NSTEMI. Indeed, data from the TIMI III registry show that patients with ST depression on the admission ECG have a 2.5 fold increase in risk of death or myocardial infarction at one year (Cannon 1997). In the ICTUS and TACTICS-TIMI 18 trials, ST depression was an independent predictor for failure of medical therapy in the conservative strategy (Sabatine 2006; Windhausen 2007b). As discussed above, post-hoc analysis of FRISC-II data showed that the benefit of an early invasive strategy on the end-point of death or non-fatal myocardial infarction only reached statistical significance in patients with ST depression on the admission ECG. In FRISC-II and the TIMI III registry, the prevalence of triple vessel or left main artery disease was approximately 50% and 66%, respectively, in patients who had ST depression on the admission ECG. Similarly, the TACTICS-TIMI 18 study reported an odds ratio for three vessel disease of 1.79 in participants with ST deviation of 0.05 to 0.09 mV, and an odds ratio of 1.91 in those with ST deviation > 0.10 mv compared to those with ST deviation < 0.05 mV. Hence, the ECG can be used as a tool to identify patients that are likely to benefit from revascularization. An analysis of the FRISC-II data showed that ST depression was still a predictor of benefit from an invasive strategy even after baseline differences were accounted for (Holmvang 2003). Further, this analysis also suggested that the benefits of the invasive strategy were further amplified with increasing amplitude of ST depression in an increasing number of ECG leads.

Data from TACTICS-TIMI 18 confirms the utility of ST segment changes in identifying a higher risk population that may benefit from an invasive strategy. Unfortunately, data could not be obtained for the end-point of death or non-fatal myocardial infarction but the study includes data for the end-point of death or non-fatal myocardial infarction or rehospitalization for ACS. Using this end-point, the RR was 0.62 (95% CI 0.53 to 0.74) in participants with baseline ST changes while a null effect was observed in those without such changes. The ICTUS data show a trend to decreased rates of (spontaneous) myocardial infarction at one year in those randomized to an early invasive strategy; relative risk ratio of 0.74 (95% CI 0.40 to 1.38). However, the events were few and CIs wide. The percentage of trial participants with ST depression on index ECG is described in Table 1; however data for subgroup analysis were not provided in all the included studies. While subgroup analyses of ST depression and troponin status may identify populations with increased risk and hence an increased power to detect statistical significance, such post hoc analyses should be interpreted with caution.

Gender

There were disparate findings between Analysis 2 and Analysis 3 on the impact of gender on outcomes. TACTICS-TIMI 18 found no significant interaction between gender and outcomes based on treatment strategy. This was contrary to the findings of Analysis 3 which showed that benefit from the invasive strategy only reached statistical significance in males. In the combined analysis (Analysis 1), gender subanalysis for intermediate death or non-fatal myocardial infarction showed that the benefit of the invasive strategy was confined to males who showed a significant 32% RR reduction. However, the number of women in the included studies was small and this decreased power to detect benefit from an invasive strategy is highlighted by the wide CIs. Women with UA/NSTEMI differ from men with the condition and this warrants further discussion. In the included studies women exhibited less severe coronary artery disease and were less likely to have elevated troponin when compared to men (Clayton 2004; Glaser 2002; Lagerqvist 2001). Further, in FRISC-II and RITA-3 women in the conservative arm had a better prognosis than men in the conservative arm. There is no a priori reason why the finding of a significant 2.1 fold RR of peri-procedural myocardial infarction in the invasive arm would not also apply to women despite their less extensive CAD on angiography. However, no such hazard was observed in TACTICS-TIMI 18, possibly because tirofiban was used upstream of invasive procedures. A retrospective analysis of TACTICS-TIMI 18 data suggests that, after adjusting for differences in baseline characteristics, the benefits of an early invasive strategy in women were the same as those seen in men (Glaser 2002). In contrast, similar analyses undertaken by FRISC-II and RITA-3 investigators did not show a benefit for the invasive strategy in women even after adjustment for baseline characteristics. The RITA-3 analysis suggested that women had better outcomes than men when managed conservatively and did not benefit from an invasive strategy even when women with high risk features were analysed separately (Clayton 2004). Women in TACTICS-TIMI 18 and RITA-3 were less likely than men to undergo CABG, even when adjusted for the presence of three vessel disease or left anterior descending artery disease (Clayton 2004; Glaser 2002). Notably in FRISC-II where the rates of CABG were similar in both men and women, the one-year mortality rate in patients undergoing CABG was 9.9% in women compared to 1.2% in men (Lagerqvist 2001). Higher operative CABG mortality has been observed in women enrolled in observational studies and this discrepancy could not be accounted for by age, co-morbidities or smaller body surface area (Blankstein 2005). The retrospective analyses from the included studies should be interpreted with appropriate caution. They highlight the importance of further research into this topic and the importance of

risk stratification, especially in women who are less likely to have angiographic CAD when compared to their male counterparts.

Other subgroups

Other subgroups of interest that were not prespecified by our protocol are discussed as a narrative review in this section. The elderly (aged > 65 years) comprise the majority of hospital admissions for UA/NSTEMI. Given that the elderly have a higher risk of recurrent events than their younger counterparts, this increased absolute risk may translate into a greater absolute risk reduction with an invasive strategy compared to a conservative strategy (Bach 2004). A retrospective analysis of the TACTICS-TIMI 18 trial showed that those aged > 65 years were more likely to have high risk features such as elevated troponins, ST deviation, diabetes and congestive heart failure (Bach 2004). Indeed, 90% of those aged > 65 years had intermediate to high risk TIMI scores (score $\geq$ 3) while 63% of those aged < 65 years had intermediate to high risk TIMI scores. The early invasivse strategy reduced early and intermediate death or myocardial infarction, with relative risk ratios of 0.58 (95% CI 0.37 to 0.92) and 0.64 (95% CI 0.45 to 0.93) respectively. The invasive strategy did not significantly benefit those aged < 65 years although the CIs were wide and overlapped. The benefits of the invasive strategy were also highly statistically significant in those aged > 75 years. However, major bleeding was increased with the invasive strategy in those aged > 65 years (RR of 1.74, 95% CI 1.12 to 2.70) while no such hazard was observed in those aged < 65 years.

Reassuringly, stroke was not increased with an invasive strategy in the elderly, showing a trend to decreased events with an early invasive strategy. The results of this type of analysis are hardly surprising given that the elderly are at increased risk of events and, therefore, a retrospective analysis will have greater power to find benefit for an intervention with absolute event rates.

The FRISC-II investigators also published relative risk estimates for patients aged greater than or less than 65 years and while the risk estimate was only significant in those aged > 65 years, the risk estimate for those < 65 years was similar and the CIs overlapped (Lagerqvist 2006). However, the results from TACTICS-TIMI 18 and FRISC-II differ from older excluded studies such as TIMI 3b, which showed a significant hazard of intervention in the younger trial participants (Anderson 1995). This point again reinforces the reasoning behind only including studies that were undertaken in the stent era since older studies are not relevant to contemporary practice.

The American Heart Association statement on coronary care in the elderly endorses an early invasive strategy for elderly patients (Alexander 2007). Moreover, since elderly patients recruited into clinical trials have fewer cardiovascular risk factors, fewer co-morbidities, better hemodynamic and renal function than community-dwelling elderly, event rates and benefit from an early invasive strategy may be even greater in the 'real world'. Registry data supports the use of the early invasive strategy in the elderly and there is no stroke hazard as a consequence of intervention reported in contemporary registries (Bauer 2007).

However, in the real world acute coronary care for the elderly is provided within the health context and co-morbid status of the patient. These factors also need to be considered for therapeutic decision-making. Despite the lack of statisitcally significant benefit with an invasive strategy in young age groups, this is not to say that young patient with high risk features would not benefit from an early invasive approach. Age is incorporated into the TIMI risk score, which integrates several prognostic variables readily available from the clinical history and first-line investigations. Similarly, retrospective analyses from the included studies have suggested that diabetes, peripheral arterial disease and a history of previous coronary artery bypass grafting are co-morbid conditions associated with an increased risk of events and hence an enhanced benefit from an early invasive strategy, with a more favorable risk-benefit ratio (Januzzi 2005; Kugelmass 2006; Norhammar 2004). However, as with age there is co-variation with other indicators of high risk. Hence while retrospective analyses focusing on a single indicator of higher risk are interesting, of greater interest is a global, easily-applicable method of risk stratification that is easily utilized by the practicing physician.

The importance of global risk stratification

As the above discussion highlights, and as subgroup analyses have illustrated, risk stratification is an integral component of managing patients with UA/NSTEMI. The goal of risk stratification is to identify patients with a high likelihood of complicated coronary artery disease who are at increased risk of recurrent coronary events or premature death and to offer such patients the benefits of revascularization. However, the clinical distinction between UA and NSTEMI does not adequately stratify high risk patients (Zaacks 1999). Consequently, the current American Heart Association (AHA) guidelines recommend the use of several parameters for risk stratification (Anderson 2007), for example the TIMI risk score (Antman 2000). To underscore this point, in a post hoc analysis of the FRISC-II data, participants with troponin T > 0.03 ng/ml as well as ST depression showed statistically significant benefit with an early invasive strategy whereas participants with only one of these variables did not (Diderholm 2002). Only TACTICS-TIMI 18 undertook subgroup analyses based on TIMI risk scores. The participants were stratified into three categories based on their TIMI risk score; at low, intermediate or high risk. The study showed that only intermediate and high risk patients benefited from the invasive strategy with regard to the primary end-point of death or non-fatal myocardial infarction or rehospitalization for ACS. Unfortunately, data for the end-point of death or non-fatal myocardial infarction were unavailable and could therefore not be incorporated into this review.

The TIMI score was extracted from the unfractionated heparin

arm of the TIMI 11B trial (TIMI 11B 1999) and was validated in the enoxaparin arm of TIMI 11B and in both arms of the ESSENCE (ESSENCE 1997) trial. The risk score was shown to be a valid predictor of all-cause mortality, myocardial infarction or urgent revascularization within 14 days of randomization. Importantly, the TIMI score was also a predictor for each of the components of this composite end-point (Antman 2000). The TIMI risk score has been subsequently validated in the TIMI III registry of unselected UA/NSTEMI patients and was shown to predict the end-point of death, myocardial infarction or recurrent ischemia and the components of the composite outcome at six weeks and one year (Scirica 2002). Further, the TIMI risk score was validated for the death, myocardial infarction or recurrent ischemia end-point at up to six months in the PRISM-PLUS trial and was also shown to predict benefit from tirofiban, even in patients with negative CK-MB (Morrow 2002). Hence, this versatile risk score is able to identify patients with high event rates who may also benefit from an invasive strategy. Intuitively, one would expect that patients with higher TIMI scores, and therefore a higher risk for mortality and recurrent events, have more extensive CAD on angiography. This has been confirmed in a retrospective analysis of patients with UA/NSTEMI (Garcia 2004). These findings were also confirmed by a retrospective analysis by the PRISM-PLUS investigators who showed the TIMI score to correlate with impaired epicardial artery blood flow and the presence of visible thrombus on angiography (Mega 2005). Although there are other published risk scores for UA/NSTEMI (Goncalves 2005), the TIMI risk score is perhaps the most widely used. Further, the low event rates in ICTUS, which exclusively enrolled troponin-positive patients, highlight the importance of considering multiple variables in risk stratification. Indeed, on five-year follow up by the RITA-3 investigators, nine factors other than treatment group emerged as multi-variate predictors of death or non-fatal myocardial infarction (Fox 2005). When the logistic coefficients for the risk factors were added and the study population divided into quartile based on risk score, patients in the highest quartile of risk score showed substantially more benefit from an invasive strategy. Similarly, the FRISC-II investigators developed a FRISC score that comprises the addition of one point for each of seven factors. These are age > 70 years, male sex, diabetes, previous MI, ST depression, increased troponin and increased interleukin-6 or C-reactive protein (Lagerqvist 2005). Having a medium to high risk (score of 3 to 7) predicted benefit from an early invasive strategy, with relative risks of 0.64 (95% CI 0.51 to 0.80) at two years and 0.75 (95% CI 0.64 to 0.89) at five years for the composite end-point of death or non-fatal myocardial infarction (FRISC-II). Low risk patients (score 0 to 2) did not benefit and had a trend to harm for the composite end-point of death or non-fatal myocardial infarction, with RR of 1.62 (95% CI 0.71 to 3.69) at two years and 1.26 (95% CI 0.66 to 2.40) at five years (FRISC-II). In contrast, the ICTUS investigators confirmed the prognostic utility of the FRISC score but were unable to predict benefit from an early invasive strategy in this trial; even the patients with the highest FRISC scores (5 to 7) derived no benefit from an early invasive strategy (RR 1.30, 95% CI 0.69 to 2.47) for the late death or myocardial infarction end-point.

Current 'real world' event rates in patients with UA/NSTEMI compared to rates observed in the included trials

The GRACE registry, which collects data from 14 countries, has reported mortality rates at six months post-discharge in patients hospitalized with various forms of acute coronary syndrome. Entry criteria for this registry include a history of chest pain and one of the following, ischemic ECG changes, increased cardiac biomarkers or a documented history of CAD. The in-hospital mortality rates for patients recruited between 1999 to 2002 were 5.9% for patients with NSTEMI and 2.7% for patients with unstable angina. Also, the six-month post-discharge mortality rates were 6.2% and 3.6% for NSTEMI and unstable angina, respectively (Goldberg 2005). Further, rehospitalization rates at six months post-discharge were about 20%. In another report from the GRACE registry that included patients recruited between 1999 and 2003, the six-month post-discharge mortality rates were reported as 11.6% for NSTEMI and 6.8% for unstable angina (Van de Werf 2005). Clearly, the mortality rates from this real-world registry are higher than those observed in the included studies as shown in Table 1. However, these patients did not receive optimal medical management in that only approximately 50% of NSTEMI patients received ACE inhibitors, heparin or statins (Goldberg 2005). While > 90% of patients received aspirin and > 80% received beta blockers, only 25% received glycoprotein IIb/IIIa receptor antagonists and it is likely few would have received clopidogrel as the patients studied were entered into the registry prior to the publication of the CURE trial (CURE 2001). That is, before use of clopidogrel for UA/NSTEMI became accepted as standard therapy. Similarly, patients enrolled in UA/NSTEMI trials received higher rates of medical therapy than patients enrolled in the CRUSADE registry (Kandzari 2005). However, the discrepancy in mortality rates between the participants in the included studies of this review and registry reported mortality rates is arguably too high to be explained by advances in medical management of UA/NSTEMI alone. Another explanation may be that selection and recruitment protocols may bias trials to enrolling patients with a risk lower than that seen in unselected patients entered into registries. While analysis of available data suggests that high risk patients may benefit from an invasive strategy, this absolute benefit is likely to narrow as early medical therapies and risk stratification procedures for UA/NSTEMI improve, combined with appropriate use of deferred coronary angiography and revascularization. This is the message arising from ICTUS which constitutes the most contemporary trial and promoted optimal medical management and risk stratification. In light of ICTUS, the current (2007) AHA guidelines endorse the option of treating stabilized but high risk (for example

troponin-positive) patients with a conservative strategy (Class IIb recommendation) (Anderson 2007). This contrasts with the previous version of the AHA guidelines which only endorsed an invasive strategy for patients with high risk features (Braunwald 2002). This is what the European guidelines continue to recommend (Bassand 2007). Novel medical therapies, like prasugrel instead of clopidogrel (TRITON-TIMI 38 2007), continue to decrease absolute event rates in patients with UA/NSTEMI and hence future trials of invasive versus conservative management for UA/NSETMI will be required as novel medical therapies are adopted. It is likely that only progressively higher risk patients will continue to benefit from early invasive intervention in the future. A report from the GRACE registry has shown that increasing use of evidence-based therapies has translated into reduced event rates with time (Fox 2007b). However, lack of benefit in regard to several end-points in this review may be due to lower risk patients being selected for trial enrolment.

The general paucity of enrolment of patients with cardiogenic shock or advanced Killip class in the included studies may mean that the results of this systematic review are not applicable to this high risk subset. Advanced Killip class has been identified as an independent predictor of mortality in patients with NSTEMI (Khot 2003), while Killip class and congestive heart failure (development of or history of) were shown to predict death or the composite of death or myocardial infarction in the GRACE registry (Fox 2006). Indeed, the current ACC/AHA guidelines for UA/NSTEMI recommend the use of features of heart failure as markers of increased risk (Anderson 2007). However, most of the included studies do not report Killip class, ejection fraction or brain natriuretic peptides in their baseline characteristics; and the event rates in the included studies indicate that patients with cardiogenic shock were not included. An exception to this is the FRISC-II trial where 13% of participants were reported to have an ejection fraction of < 45% at baseline and the VINO trial where 53% of the population were reported to have a baseline Killip class of II or III. This high percentage of patients with pulmonary edema in VINO may explain why this trial had the highest standardized mortality rates of the included studies (Table 1) and, while being a small trial, found a robust benefit for an early invasive strategy. Observational data have shown Killip class II and III patients to have significant mortality benefit (at 30 days and 6 months) from an invasive strategy while patients with Killip class I do not benefit (Rott 2001). The SHOCK 1999 trial (n = 302), which recruited STEMI patients with cardiogenic shock, found a significant mortalty benefit for an early invasive strategy compared to a conservative strategy at six months, with mortality rates being 50.3% and 63.1% (P = 0.027) respectively (SHOCK 1999). These are consistent with observations from the GRACE registry (Dauerman 2002). Similarly, elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) has been shown to predict a poor prognosis in patients with UA/NSTEMI independently of age, Killip class or left ventricular ejection fraction (Jernberg 2004). In a retrospective subgroup analyses from FRISC-II (n = 2017), NT-pronBNP measured at median 39 hours from symptom presentation correlated with TnT (r = 0.53, P < 0.001), interleukin-6 (r = 0.29, P < 0.001) and severity of coronary disease on angiography (Jernberg 2003). The relationship between higher BNP and more severe angiographic coronary disease was also found in a small retrospective analysis from the TACTICS-TIMI 18 trial which also showed higher BNP to be associated with higher TIMI frame counts, consistent with reduced myocardial perfusion perfusion (Sadanandan 2004). In FRISC-II, NT-proBNP predicted two-year mortality independently of TnT, interleukin-6 and left ventricular ejection fraction in this cohort but did not predict the incidence of myocardial infarction. Importantly, this retrospective subgroup analysis from the FRISC-II investigators suggested that the early invasive strategy only improved two-year mortality in patients in the highest tertile of NT-proBNP (> 906 ng/L for men, > 1345 ng/L for women) and with an interleukin-6 concentration > 5ng/ml (absolute risk reduction of 7.3%; RR 0.46, 95% CI 0.21 to 1.00). Such retrospective analyses are hypothesis generating and by no means definitive. A similar analysis from TACTICS TIMI18 (n = 1676) measured BNP instead of NT-proBNP and dichotomized patients at a BNP of > 80 ng/L. The analysis found that patients with elevated BNP had higher seven-day and six-month mortality (2.5% versus 0.7%, P < 0.01; and 8.4% versus 1.8%, P < 0.01 respectively) but BNP was not shown to predict benefit of an invasive strategy (Morrow 2003). This may be due to the relatively short follow up of the TACTICS TIMI18 study, which was only six months (Table 1). The ICTUS investigators also examined the prognostic influence of NT-proBNP measured at median 13 hours from presentation in a 1141 patient subgroup from the main trial (Windhausen 2007a). In the highest quartile (> 1170 ng/L for men, > 2150 ng/L for women) one-year mortality was 7.3% compared to 1.1% for patients in the lower three quartiles. However, as with the retrospective analyses from FRISC-II and TACTICS-TIMI 18, NT-proBNP failed to predict myocardial infarction and, in contrast to FRISC-II, elevated NT-proBNP did not predict benefit from an early invasive strategy in the ICTUS cohort (Windhausen 2007a). Hence, the role of natriuretic peptides and assessment of patients for clinical features of congestive heart failure in UA/NSTEMI need to be further elucidated. In the interim, patients with features of congestive heart failure need to be considered at high risk for death and managed with aggressive therapy.

The GRACE investigators determined predictors of a poor prognosis which were derived from and validated in cohorts enrolled in GRACE between 1999 to 2002 and 2002 to --2003 respectively (Eagle 2004). The investigators identified nine variables. These were older age, history of myocardial infarction, history of heart failure, increased heart rate, lower systolic blood pressure, elevated creatinine, elevated cardiac biomarkers, ST depression and not having PCI as independent predictors of increased six-month mortality across the ACS spectrum. Importantly, the GRACE risk

score incorporates renal function, which is an important and practical risk prognosticator in UA/NSTEMI that was not considered during the derivation of the TIMI risk score (Antman 2000). In a retrospective subgroup analysis of the FRISC-II trial, creatinine clearance was estimated from serum creatinine with the Cockcroft-Gault formula (Johnston 2006). In the conservatively managed patients, the rates of death or myocardial infarction for creatinine clearances of < 69 mL/min, 69 to 90 mL/min and > 90 mL/min were 22.4%, 14.6% and 11.6%, respectively. The corresponding event rates in the invasive strategy were 14.6% (P < 0.01 versus conservative), 9.9% (P = 0.048 versus conservative) and 11.2%, respectively. Indeed, there was a significant interaction between treatment strategy and outcomes in patients with a creatinine clearance of < 90 mL/min. These data are indeed sobering since patients with renal dysfunction are often denied aggressive therapy in the real world, possibly because of clinician concerns about bleeding risk and a poor prognosis regardless of therapy. These data are particularly relevant to clinicians practicing in countries where an estimate of glomerular filtration rate is mandatory on adult electrolyte panels, as is standard in the United States and Australia. Hence, risk stratification is an integral part of the management of patients with UA/NSTEMI and needs to be considered carefully in future prospective randomized controlled trials on the topic. Further, the role of estimated glomerular filtration rate and NT-proBNP in risk prognotication over and above established markers such as the TIMI risk score need to be further evaluated.

Current 'real world' management of patients with UA/NSTEMI with emphasis on the relationship between patient risk and subsequent management

Despite the extensive literature on risk stratification, real-world data from the GRACE registry has shown that high risk patients are no more likely to receive enoxaparin, glycoprotein IIb/IIIa receptor antagonists or to undergo catheterization and PCI than low risk patients (Oliveira 2007). In a different analysis from the GRACE registry that only included patients recruited with direct access to a catheterization laboratory, an inverse relationship was found between the level of patient risk (with the GRACE risk score) and the frequency of angiography and PCI (Fox 2007a). Indeed, the rates of cardiac catheterization in low, medium and high risk patients with UA/NSTEMI were 72%, 68% and 51% respectively, while the rates of PCI were 40%, 35% and 25% respectively. Further, thienopyridines and glycoprotein IIb/IIIa receptor antagonists were more commonly used in low risk patients than medium or high risk patients with similar findings in a Canadian registry (Yan 2007). Likewise, diabetics are a higher risk cohort that are not treated more aggressively than non-diabetics with UA/NSTEMI (Franklin 2004). The reasons for the discrepancy between patient risk and treatment have been unclear but recent data from a Canadian registry suggests that the most common reason for under-utilization of an invasive strategy in high risk patients is under-estimation of patient risk by the treating physician (Lee 2008). In this regard, a focused initiative to educate physicians on risk stratfication may yield results in improving quality of care in patients with UA/NSTEMI.

Quality of life end-points

Although not an initial outcome of this systematic review, this section herein provides a narrative discussion of health-related quality of life (HRQOL) outcomes. Four studies specifically investigated health-related quality of life (HRQOL) and functional status following invasive management for non-STEMI compared to non-invasive management. One was a trial which had changes in QOL as a primary end-point and the other three were analyses from included studies where HRQOL measures were secondary end-points. In the primary end-point trial, involving only 88 patients (Eisenberg 2005), there was no difference between groups at 12 months in peak exercise reached on an endurance exercise treadmill (7.8 versus 6.7 metabolic equivalents). Functional status was improved in the invasive group (Duke Activity Status Index scores 4.3 versus -3.5, P = 0.04) as was angina-specific quality of life measured by the Seattle Angina Questionnaire measure of anginal stability (21.6 versus -5.3, P = 0.020), anginal frequency (22.9 versus 2.3, P = 0.02) and treatment satisfaction (11.2 versus -10.3, P = 0.02).

In the RITA-3 trial (Kim 2005), HRQOL was assessed with the Short Form-36 (SF-36), Seattle Angina Questionnaire (SAQ), EuroQOL Visual Analogue Scale (EQ-VAS) and EuroQOL 5-Dimensional Classification (EQ-5D) at baseline, four-month and one-year follow up. Mean changes from baseline EQ-VAS scores were better for the invasive versus non-invasive strategy at four months (treatment difference of 3.0, P < 0.001) and one year (2.3, P < 0.01). The EQ-5D utility scores were also higher for the invasive group at four months (treatment difference 0.036, P < 0.01) but not at one year (0.016, P = 0.20). For SF-36, the invasive strategy scored significantly better at four months for physical function, physical role function, emotional role function, social function, vitality and general health. The SAQ scores for exertional capacity, anginal stability and frequency, treatment satisfaction and disease perception were significantly better for the invasive strategy at both four months and one year, although attenuated at the last follow up. The authors concluded that improvements in HRQOL for the invasive strategy were most likely due to improvements in anginal symptoms.

In the FRISC II trial (Janzon 2004), HRQOL was measured using the generic Medical Outcomes Study Short Form 36 (SF-36) and the disease-specific Angina Pectoris Quality of Life Questionnaire (APQLQ) at baseline and three, six and 12 months follow up. The invasively treated group showed a significantly better quality of life in all eight scales and both component scores (physical and mental) of the SF-36 at three and six-month follow up (P < 0.01) compared with the non-invasively treated group. These differences

remained at 12-month follow up, with significance in seven of the scales and in the physical component score. The invasive group scored significantly more highly on all five subscales of the APQLQ scores at three months ($P < 0.01$), on four subscales at six months ($P < 0.05$) but only on one subscale at one year.

The TACTICS-TIMI 18 trial (Weintraub 1999) planned to assess health status using some measure of utility in order to perform cost-effectiveness evaluations of invasive versus non-invasive strategy but subsequent publications (Mahoney 2002) failed to disclose HRQOL data. From the available evidence it would appear that improvements in HRQOL as a result of an invasive strategy are modest and last on average no more than 12 months, with anginal relief being the key determinant of improved HRQOL.

Findings from studies in the pre-stent era and other reviews on this topic

We excluded two large trials that were undertaken in the pre-stent era (TIMI-3b 1995; VANQWISH 1998). The early invasive arm of TIMI-3b 1995 involved cardiac catheterization at an average 36 hours of randomization and coronary revascularization by coronary angioplasty or CABG. The early invasive strategy had no effect on hard clinical end-points of death, myocardial infarction, stroke or the composite of death or myocardial infarction. As is consistent with more recent clinical trials, the early invasive strategy reduced recurrent hospitalization at both six weeks and one year, with RR of 0.54 (95% CI 0.40 to 0.74) and 0.79 (95% CI 0.68 to 0.93) respectively (TIMI-3b 1995). In TIMI-3b 1995 an early invasive strategy did not reduce the need for angina medications at one year. In contrast, the VANQWISH study showed a hazard associated with the early invasive strategy, which involved cardiac catheterization at an average 48 hours after randomization. Indeed, the early invasive strategy was associated with an increased relative risk of mortality at hospital discharge, one month and one year (RR of 3.47 (95% CI 1.41 to 8.52; 2.53, 95% CI 1.19 to 5.42; and 1.60, 95% CI 1.08 to 2.37 respectively) (VANQWISH 1998). Similarly, a hazard was associated with the early invasive strategy for the composite end-point of death or non-fatal myocardial infarction. The hazard of an early invasive strategy on these end-points ceased to be significant by the end of the study (average 23 months). Forty-four per cent of patients in the invasive arm of this trial underwent a revascularization procedure, 47% involving CABG. The mortality associated with CABG in the invasive arm was 11.6% compared to 3.4% in the conservative arm.This discrepancy has been cited as an explanation for the increased mortality in the early invasive arm of the VANQWISH trial (Braunwald 2003). Not surprisingly, rates of background medical therapy were low by contemporary standards; glycoprotein IIb/IIIa receptor antagonists, ticlopidine or statins were not routinely used.

Two older meta-analyses on this topic that included the aforementioned old trials and trials that we excluded for reasons other than low stent use reached different conclusions to the ones presented here (Choudhry 2005; Mehta 2005). These reviews did not include the most recent trial, the ICTUS study, although a subsequent meta-analysis included the early trials and the one-year results from ICTUS (Bavry 2006). The review by Mehta et al showed that an invasive strategy was associated with a mortality hazard from randomization to hospital discharge (RR 1.61, 95% CI 1.14 to 2.27) (Mehta 2005). An early hazard with an invasive strategy was not found in this review, possibly because outdated studies were excluded. When Mehta et al analysed outcomes from hospital discharge to end of follow up, the early invasive strategy was associated with reductions in death and reductions in non-fatal myocardial infarction (RR of 0.78, 95% CI 0.64 to 0.94; and 0.56, 95% CI 0.47 to 0.68 respectively). When Mehta et al analysed trial data from randomization to end of follow up, the invasive strategy had a null effect on mortality but a reduction in non-fatal myocardial infarction (RR 0.77, 95% CI 0.67 to 0.89). This is consistent with the finding of this review. This review analysed the end-points at certain time points since it was felt that combining outcomes collected from studies with short duration (six months) with those of long duration (five years) would not provide a meaningful point estimate (see table 'Caracteristics of included studies'). A significant reduction in recurrent angina and rehospitalization with an invasive strategy was a consistent finding across all reviews (Bavry 2006; Choudhry 2005; Mehta 2005). More recently, a meta-regression analysis that included the earlier studies but which excluded VANQWISH 1998 showed that the benefit of the invasive strategy with respect to the end-point of death or the composite of death or myocardial infarction to be related to the comparator odds ratio for events in the conservative group (Tarantini 2007). This implies that the benefit of the invasive strategy relates to the baseline risk in the comparator group. One meta-analysis has been published since the publication of late follow up from the ICTUS trial and this report, which included the older studies, found no benefit of an invasive strategy on the end-points of death, myocardial infarction or the composite of death or myocardial infarction (Qayyum 2008). The findings from our analysis differ because we excluded older studies and utilized the reported 'spontaneous' myocardial infarction end-point for our analysis in light of the controversy surrounding the routine peri-procedural biomarker assessment undertaken by the ICTUS investigators.

AUTHORS' CONCLUSIONS

Implications for practice

The most consistent and robust findings of this review are that an invasive strategy in UA/NSTEMI results in a significant 33% relative risk reduction for both the end-points of refractory angina and rehospitalization at six to 12 months. While the invasive strategy is associated with a two fold increase in the risk of peri-procedural

myocardial infarction, the available data suggest a significant 27% and 22% relative risk reduction in the rate of myocardial infarction assessed at six to 12 months and three to five years, respectively. Hence the early hazard associated with a routine invasive strategy must be weighed against potential long term benefit in clinical end-points. However, longer term follow up of more contemporary trials may show this benefit to be attenuated by more optimal use of medical therapies and deployment of more rigorous risk stratification protocols in the days immediately following onset of the acute event. The benefits of an early invasive strategy may be more meaningful in higher risk patients who would be expected to have a lower number needed to treat. The data presented in this review suggest that an early invasive strategy is superior to a conservative strategy. Larger trials with greater power for mortality end-points are required. For illustrative purposes, the weighted average mortality in the conservative arm of included studies was 10.1% by end of follow up. The power to detect a 10% difference between the treatment strategies with the included number of patients is only 27%. Hence, more data is required before firm conclusions regarding the benefits and harms of an invasive strategy on mortality can be reached.

Implications for research

This review has highlighted the need for further research on treatment strategies for UA/NSTEMI. The trials have enrolled heterogeneous populations of patients with variable levels of risks and event rates, subject to varying co-interventions, and using outcome measures subject to variable definition and timing. Risk stratification of the participants in each trial based on a validated risk system (for example the TIMI risk score) would allow for more meaningful meta-analyses of available data and provide a risk score or an absolute event rate above which an invasive strategy is expected to significantly improve outcomes. Clearly as medical therapies for UA/NSTEMI improve, progressively less absolute benefit is to be gained by intervention and hence the risk at which invasive intervention is warranted is likely to represent a moving target. Another major limitation to the analyses undertaken in this review is the underpowering of trials regarding the effects of an invasive strategy on all-cause mortality due to the short length of follow up and in interpretation of sub-group analyses. This could be addressed in future clinical trials by ensuring sufficient events to accrue by way of either larger sample sizes, enrolment of higher risk patients or longer follow up. Finally, further research is required to better define the benefits and hazards of an invasive strategy in females.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

FRISC-II

Methods	randomization: an independent organization randomized patients using telefax blinding: non-blinded selection bias, intention-to-treat analysis: 9.7% lost to follow up at five years; intention-to-treat analysis used
Participants	2457 patients with anginal pain within the last 48 hours and ST depression or elevated cardiac markers overall impression of patient risk level: intermediate-high
Interventions	conservative arm: aspirin, beta blocker, statin, ACEI, dalteparin or UFH invasive arm: as above and routine angiography (average time to angiography: 4d). 10% glycoprotein 2b/3a receptor antagonist use
Outcomes	death all causes (6, 12, 24 months, 5 years), MI (6, 12, 24 months, 5 years), refractory angina (6 months), death or non-fatal MI (6, 12, 24 months, 5 years), rehospitalization (6 weeks, 6 , 12 months), procedural MI, bleeding, contrast allergy
Notes	

ICTUS

Methods	randomization: centralized system; randomized by telephone blinding: end-points were adjudicated by a blinded committee selection bias, intention-to-treat analysis: five patients lost to follow up; intention-to-treat analysis used
Participants	1200 patients with accelerating angina or angina at rest in the preceding 24 hours and an elevated cardiac troponin T >0.3 µg/litre AND either ischemic ECG changes OR documented history of CAD (previous catheterization, history of myocardial infarction or positive exercise test) Overall impression on level of risk in patients: high risk; all patients had a positive troponin test on randomization
Interventions	conservative arm: aspirin, enoxaparin, statin, clopidogrel invasive arm: as above, abciximab and routine angiography (median time to angiography: 23 hours) post-randomization. 94% glycoprotein 2b/3a receptor antagonist use
Outcomes	death all causes (1, 3, 4 years), MI (1, 3 year), rehospitalization (1, 3 years)
Notes	

RITA-3

Methods	randomization: central telephone service blinding: open selection bias, intention-to-treat analysis: all patients accounted for at 2 years; intention-to-treat analysis used. While 99.8% of patients were followed up for at least 3 years, this figure was 59% at 5 years
Participants	1810 patients with chest pain within the last 72 hours, a documented history of coronary artery disease (CAD) and one of the following: ischemic ECG changes or Q waves suggesting previous MI or proven CAD on angiogram. Excluded those with probable evolving MI or those with elevated enzymes (2x) before randomization. Overall impression on level of risk in patients: Intermediate
Interventions	conservative arm: aspirin, beta blocker, enoxaparin invasive arm: as above and routine angiography (median time to angiography: 2days). 25% glycoprotein 2b/3a receptor antagonist use
Outcomes	death all causes (4, 12, 24 months, 5 years), MI (4, 12, 24 months, 5 years), refractory angina (4,12 mo), death or non-fatal MI (4, 12, 24 months, 5 years), procedural bleeding & MI
Notes	

TACTICS-TIMI 18

Methods	randomization: centralized system blinding: end points were adjudicated by a blinded committee selection bias, intention-to-treat analysis: all patients accounted for by end of trial; intention-to-treat analysis used
Participants	2220 patients with angina (accelerating or prolonged) at rest in preceding 24 hours & at least one of the following: ischemic ECG changes, elevated cardiac markers or documented CAD (previous catheterization, revasc or MI) Overall impression on level of risk in patients:variable; sub analyses reported on TIMI risk score and troponin status
Interventions	conservative arm: aspirin, beta blocker, UFH, tirofiban, statin invasive arm: as above and routine angiography (median time to angiography: 22hours). 94% glycoprotein 2b/3a receptor antagonist use
Outcomes	death all causes (30 days, 6 months), refractory angina (6 months), death or MI (30 days, 6 months), rehospitalization (30 days, 6 months)
Notes	

VINO

Methods	randomization: sealed envelopes blinding: open selection bias, intention-to-treat analysis: all patients accounted for by end of trial; intention-to-treat analysis used
Participants	131 patients with ischemic chest pain lasting more than 20 minutes (within the preceding 24 hours) + ECG changes + elevated cardiac markers Overall impression on level of risk in patients: high; all patients were cardiac biomarker positive

VINO (*Continued*)

Interventions	conservative arm: aspirin, beta blocker, UFH, invasive arm: as above & routine angiography (average time to angiography: 6.2hours). 0% glycoprotein 2b/3a receptor antagonist use
Outcomes	death all causes (30 days, 6 months), MI (30 days, 6 months), death or non-fatal MI (30 days, 6 months), rehospitalization (30 days, 6 months)
Notes	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Eisenberg 2005	This trial included patients with STEMI and while index and late death are reported, outcomes for UA/NSTEMI are not reported separately. Also, this was a trial of 88 patients where the primary end-points related to quality of life
GUSTO2b 2003	This was a post-hoc analysis from a trial designed to compare hirudin to heparin in UA/NSTEMI patients
MATE 1998	This trial was undertaken in the pre-stent era & included patients with STEMI
MITI 2000	This was not a randomized clinical trial. The data are extracted from a registry
Neumann 2003	This trial included UA/NSTEMI patients that were all due to have angiography. This trial compared 2 invasive strategies depending on whether angiography was undertaken at <6hours or at 3-5 days. Hence, this trial compared two different invasive strategies i.e. early or delayed invasive and is not appropriate for this review
TIMI-3b 1995	This trial was undertaken in the pre-stent era.
TRUCS 2000	This trial was deemed inappropriate to this review since the patients included were admitted with recurrent angina 48 hours after the index case of unstable angina. Hence, the patients in this trial had all been managed conservatively for at least 48 hours after their index chest pain & had to suffer another bout of angina before randomization was considered. Studies included in this review require that patients are randomized at index presentation. This study, by definition, only considered patients with Braunwald class IIIb or IIIc unstable angina and is therefore dissimilar enough from the included studies to warrant exclusion
VANQWISH 1998	This trial was undertaken in the pre-stent era and included patients treated with thrombolysis
Zhao 2005	This study doesn't meet this review's stent requirement.

DATA AND ANALYSES

Comparison 1. All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Index Death	5	7781	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.98, 2.39]
1.1 Routine glycoprotein IIb/IIIa receptor antagonist use	2	3383	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.84, 3.31]
1.2 No routine glycoprotein IIb/IIIa receptor antagonist use	3	4398	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.65, 2.96]
2 Early Death	3	4161	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.66, 1.88]
2.1 Routine glycoprotein IIb/IIIa receptor antagonist use	1	2220	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.76, 2.51]
2.2 No routine glycoprotein IIb/IIIa receptor antagonist use	2	1941	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.15, 3.02]
3 Intermediate Death	5	7818	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.57, 1.19]
3.1 Routine glycoprotein IIb/IIIa receptor antagonist use	2	3420	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.66, 1.39]
3.2 No routine glycoprotein IIb/IIIa receptor antagonist use	3	4398	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.33, 1.37]
4 Late Death	3	5467	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.76, 1.08]
4.1 Routine glycoprotein IIb/IIIa receptor antagonist use	1	1200	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.74, 1.67]
4.2 No routine glycoprotein IIb/IIIa receptor antagonist use	2	4267	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.04]
5 Index Myocardial Infarction	5	7781	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.52, 2.03]
5.1 Routine glycoprotein IIb/IIIa receptor antagonist use	2	3383	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.44, 1.02]
5.2 No routine glycoprotein IIb/IIIa receptor antagonist use	3	4398	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.65, 3.12]
6 Early Myocardial Infarction	3	4161	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.38, 1.06]
6.1 Routine glycoprotein IIb/IIIa receptor antagonist use	1	2220	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.35, 0.79]
6.2 No routine glycoprotein IIb/IIIa receptor antagonist use	2	1941	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.18, 2.17]
7 Intermediate Myocardial Infarction	5	7818	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.62, 0.86]
7.1 Routine glycoprotein IIb/IIIa receptor antagonist use	2	3420	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.54, 0.96]
7.2 No routine glycoprotein IIb/IIIa receptor antagonist use	3	4398	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.52, 0.98]
8 Late Myocardial Infarction	3	5467	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.67, 0.92]
8.1 Routine glycoprotein IIb/IIIa receptor antagonist use	1	1200	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.66, 1.55]
8.2 No routine glycoprotein IIb/IIIa receptor antagonist use	2	4267	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.63, 0.90]
9 Index Death or Non-Fatal MI	4	6618	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.59, 2.21]

9.1 Routine glycoprotein IIb/IIIa receptor antagonist use	1	2220	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.51, 1.17]
9.2 No routine glycoprotein IIb/IIIa receptor antagonist use	3	4398	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.75, 2.86]
10 Early Death or Non-Fatal MI	2	2351	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.45, 0.92]
10.1 Routine glycoprotein IIb/IIIa receptor antagonist use	1	2220	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.48, 0.94]
10.2 No routine glycoprotein IIb/IIIa receptor antagonist use	1	131	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.06, 1.39]
11 Intermediate Death or Non-Fatal MI	4	6618	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.62, 0.94]
11.1 Routine glycoprotein IIb/IIIa receptor antagonist use	1	2220	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.58, 1.01]
11.2 No routine glycoprotein IIb/IIIa receptor antagonist use	3	4398	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.52, 1.04]
12 Intermediate Death or Non-Fatal MI; Gender Sub-Analysis	3	6478	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.59, 0.91]
12.1 Male	3	4297	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.57, 0.81]
12.2 Female	3	2181	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.48, 1.31]
13 Late Death or Non-Fatal MI	3	5467	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.08]
13.1 Routine glycoprotein IIb/IIIa receptor antagonist use	1	1200	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.87, 1.63]
13.2 No routine glycoprotein IIb/IIIa receptor antagonist use	2	4267	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.72, 0.92]
14 Intermediate Refractory Angina	4	7687	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.55, 0.83]
14.1 Routine glycoprotein IIb/IIIa receptor antagonist use	2	3420	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.49, 1.38]
14.2 No routine glycoprotein IIb/IIIa receptor antagonist use	2	4267	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.50, 0.64]
15 Intermediate Rehospitalization	4	6008	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.61, 0.74]
15.1 Routine glycoprotein IIb/IIIa receptor antagonist use	2	3420	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.63, 0.93]
15.2 No routine glycoprotein IIb/IIIa receptor antagonist use	2	2588	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.59, 0.71]

Comparison 2. Safety end-points

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Procedure-related MI	3	5467	Risk Ratio (M-H, Random, 95% CI)	2.00 [1.53, 2.61]
2 Bleeding	3	6487	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.27, 2.31]
3 Stroke	2	4677	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.34, 2.31]

Analysis 1.1. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 1 Index Death.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 1 Index Death

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Routine glycoprotein IIb/IIIa receptor antagonist use					
ICTUS	6/586	5/577		14.4 %	1.18 [0.36, 3.85]
TACTICS-TIMI 18	16/1114	8/1106		28.1 %	1.99 [0.85, 4.62]
Subtotal (95% CI)	**1700**	**1683**		**42.5 %**	**1.67 [0.84, 3.31]**
Total events: 22 (Invasive), 13 (Conservative)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.49$, df = 1 (P = 0.48); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.46 (P = 0.15)					
2 No routine glycoprotein IIb/IIIa receptor antagonist use					
FRISC-II	13/1222	11/1235		31.4 %	1.19 [0.54, 2.66]
RITA-3	14/895	6/915		22.1 %	2.39 [0.92, 6.18]
VINO	1/64	3/67		4.0 %	0.35 [0.04, 3.27]
Subtotal (95% CI)	**2181**	**2217**		**57.5 %**	**1.39 [0.65, 2.96]**
Total events: 28 (Invasive), 20 (Conservative)					
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 2.83$, df = 2 (P = 0.24); $I^2 = 29\%$					
Test for overall effect: Z = 0.85 (P = 0.40)					
Total (95% CI)	**3881**	**3900**		**100.0 %**	**1.53 [0.98, 2.39]**
Total events: 50 (Invasive), 33 (Conservative)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.43$, df = 4 (P = 0.49); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.85 (P = 0.064)					

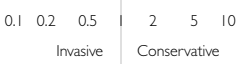
Analysis 1.2. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 2 Early Death.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 2 Early Death

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Routine glycoprotein IIb/IIIa receptor antagonist use					
TACTICS-TIMI 18	25/1114	18/1106		44.7 %	1.38 [0.76, 2.51]
Subtotal (95% CI)	**1114**	**1106**		**44.7 %**	**1.38 [0.76, 2.51]**
Total events: 25 (Invasive), 18 (Conservative)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
2 No routine glycoprotein IIb/IIIa receptor antagonist use					
RITA-3	26/895	24/915		49.5 %	1.11 [0.64, 1.91]
VINO	1/64	5/67		5.8 %	0.21 [0.03, 1.74]
Subtotal (95% CI)	**959**	**982**		**55.3 %**	**0.67 [0.15, 3.02]**
Total events: 27 (Invasive), 29 (Conservative)					
Heterogeneity: Tau^2 = 0.78; Chi^2 = 2.25, df = 1 (P = 0.13); I^2 =56%					
Test for overall effect: Z = 0.53 (P = 0.60)					
Total (95% CI)	**2073**	**2088**		**100.0 %**	**1.11 [0.66, 1.88]**
Total events: 52 (Invasive), 47 (Conservative)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 2.87, df = 2 (P = 0.24); I^2 =30%					
Test for overall effect: Z = 0.38 (P = 0.70)					



Analysis 1.3. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 3 Intermediate Death.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 3 Intermediate Death

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Routine glycoprotein IIb/IIIa receptor antagonist use					
ICTUS	15/604	15/596		16.6 %	0.99 [0.49, 2.00]
TACTICS-TIMI 18	37/1114	39/1106		26.3 %	0.94 [0.61, 1.47]
Subtotal (95% CI)	**1718**	**1702**		**42.9 %**	**0.95 [0.66, 1.39]**
Total events: 52 (Invasive), 54 (Conservative)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.91); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.24 (P = 0.81)					
2 No routine glycoprotein IIb/IIIa receptor antagonist use					
FRISC-II	27/1222	48/1235		25.3 %	0.57 [0.36, 0.90]
RITA-3	41/895	36/915		26.5 %	1.16 [0.75, 1.80]
VINO	2/64	9/67		5.3 %	0.23 [0.05, 1.04]
Subtotal (95% CI)	**2181**	**2217**		**57.1 %**	**0.67 [0.33, 1.37]**
Total events: 70 (Invasive), 93 (Conservative)					
Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 7.54$, df = 2 (P = 0.02); $I^2 = 73\%$					
Test for overall effect: Z = 1.10 (P = 0.27)					
Total (95% CI)	**3899**	**3919**		**100.0 %**	**0.82 [0.57, 1.19]**
Total events: 122 (Invasive), 147 (Conservative)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 8.15$, df = 4 (P = 0.09); $I^2 = 51\%$					
Test for overall effect: Z = 1.05 (P = 0.29)					

Analysis 1.4. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 4 Late Death.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 4 Late Death

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Routine glycoprotein IIb/IIIa receptor antagonist use					
ICTUS	45/604	40/596		16.4 %	1.11 [0.74, 1.67]
Subtotal (95% CI)	**604**	**596**		**16.4 %**	**1.11 [0.74, 1.67]**
Total events: 45 (Invasive), 40 (Conservative)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.50 (P = 0.62)					
2 No routine glycoprotein IIb/IIIa receptor antagonist use					
FRISC-II	117/1222	124/1235		42.0 %	0.95 [0.75, 1.21]
RITA-3	102/895	132/915		41.6 %	0.79 [0.62, 1.01]
Subtotal (95% CI)	**2117**	**2150**		**83.6 %**	**0.87 [0.72, 1.04]**
Total events: 219 (Invasive), 256 (Conservative)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.17$, df = 1 (P = 0.28); $I^2 = 15\%$					
Test for overall effect: Z = 1.50 (P = 0.13)					
Total (95% CI)	**2721**	**2746**		**100.0 %**	**0.90 [0.76, 1.08]**
Total events: 264 (Invasive), 296 (Conservative)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.35$, df = 2 (P = 0.31); $I^2 = 15\%$					
Test for overall effect: Z = 1.14 (P = 0.25)					

Analysis 1.5. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 5 Index Myocardial Infarction.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 5 Index Myocardial Infarction

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Routine glycoprotein IIb/IIIa receptor antagonist use					
ICTUS	9/586	9/577		19.4 %	0.98 [0.39, 2.46]
TACTICS-TIMI 18	27/1114	44/1106		26.2 %	0.61 [0.38, 0.98]
Subtotal (95% CI)	**1700**	**1683**		**45.6 %**	**0.67 [0.44, 1.02]**
Total events: 36 (Invasive), 53 (Conservative)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.83$, df = 1 (P = 0.36); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.85 (P = 0.065)					
2 No routine glycoprotein IIb/IIIa receptor antagonist use					
FRISC-II	68/1222	31/1235		26.9 %	2.22 [1.46, 3.36]
RITA-3	17/895	15/915		22.9 %	1.16 [0.58, 2.31]
VINO	0/64	3/67		4.5 %	0.15 [0.01, 2.84]
Subtotal (95% CI)	**2181**	**2217**		**54.4 %**	**1.43 [0.65, 3.12]**
Total events: 85 (Invasive), 49 (Conservative)					
Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 5.29$, df = 2 (P = 0.07); $I^2 = 62\%$					
Test for overall effect: Z = 0.89 (P = 0.38)					
Total (95% CI)	**3881**	**3900**		**100.0 %**	**1.03 [0.52, 2.03]**
Total events: 121 (Invasive), 102 (Conservative)					
Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 18.35$, df = 4 (P = 0.001); $I^2 = 78\%$					
Test for overall effect: Z = 0.08 (P = 0.93)					

Analysis 1.6. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 6 Early Myocardial Infarction.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 6 Early Myocardial Infarction

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Routine glycoprotein IIb/IIIa receptor antagonist use					
TACTICS-TIMI 18	34/1114	64/1106		50.2 %	0.53 [0.35, 0.79]
Subtotal (95% CI)	**1114**	**1106**		**50.2 %**	**0.53 [0.35, 0.79]**
Total events: 34 (Invasive), 64 (Conservative)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.08 (P = 0.0021)					
2 No routine glycoprotein IIb/IIIa receptor antagonist use					
RITA-3	30/895	34/915		44.5 %	0.90 [0.56, 1.46]
VINO	1/64	5/67		5.4 %	0.21 [0.03, 1.74]
Subtotal (95% CI)	**959**	**982**		**49.8 %**	**0.63 [0.18, 2.17]**
Total events: 31 (Invasive), 39 (Conservative)					
Heterogeneity: Tau^2 = 0.46; Chi^2 = 1.75, df = 1 (P = 0.19); I^2 =43%					
Test for overall effect: Z = 0.73 (P = 0.47)					
Total (95% CI)	**2073**	**2088**		**100.0 %**	**0.64 [0.38, 1.06]**
Total events: 65 (Invasive), 103 (Conservative)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 3.89, df = 2 (P = 0.14); I^2 =49%					
Test for overall effect: Z = 1.73 (P = 0.083)					

Analysis 1.7. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 7 Intermediate Myocardial Infarction.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 7 Intermediate Myocardial Infarction

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Routine glycoprotein IIb/IIIa receptor antagonist use					
ICTUS	22/604	27/596		9.4 %	0.80 [0.46, 1.40]
TACTICS-TIMI 18	53/1114	76/1106		24.6 %	0.69 [0.49, 0.97]
Subtotal (95% CI)	**1718**	**1702**		**33.9 %**	**0.72 [0.54, 0.96]**
Total events: 75 (Invasive), 103 (Conservative)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.20, df = 1 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 2.21 (P = 0.027)					
2 No routine glycoprotein IIb/IIIa receptor antagonist use					
FRISC-II	105/1222	143/1235		49.9 %	0.74 [0.58, 0.94]
RITA-3	34/895	44/915		14.9 %	0.79 [0.51, 1.22]
VINO	2/64	10/67		1.3 %	0.21 [0.05, 0.92]
Subtotal (95% CI)	**2181**	**2217**		**66.1 %**	**0.72 [0.52, 0.98]**
Total events: 141 (Invasive), 197 (Conservative)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 2.89, df = 2 (P = 0.24); I^2 =31%					
Test for overall effect: Z = 2.07 (P = 0.038)					
Total (95% CI)	**3899**	**3919**		**100.0 %**	**0.73 [0.62, 0.86]**
Total events: 216 (Invasive), 300 (Conservative)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.10, df = 4 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 3.66 (P = 0.00026)					

Analysis 1.8. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 8 Late Myocardial Infarction.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 8 Late Myocardial Infarction

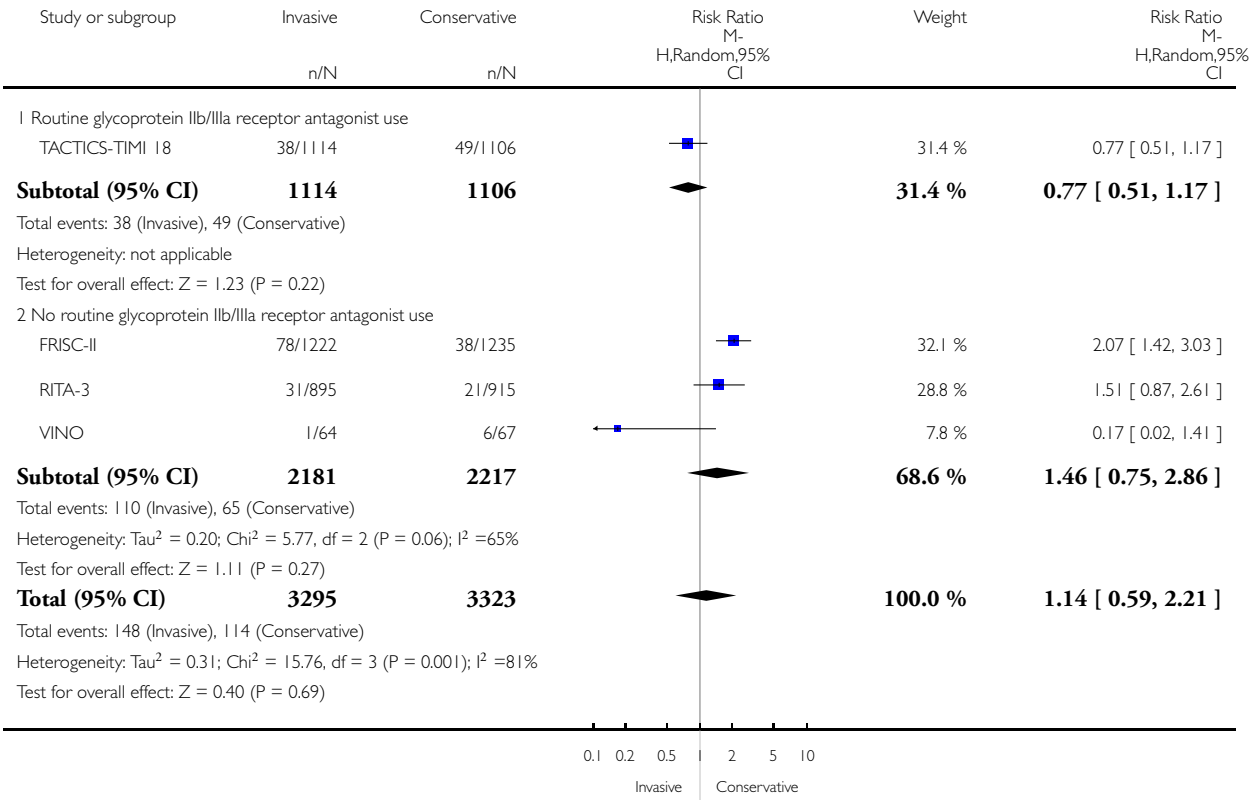
Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Routine glycoprotein IIb/IIIa receptor antagonist use					
ICTUS	40/604	39/596		14.8 %	1.01 [0.66, 1.55]
Subtotal (95% CI)	**604**	**596**		**14.8 %**	**1.01 [0.66, 1.55]**
Total events: 40 (Invasive), 39 (Conservative)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.96)					
2 No routine glycoprotein IIb/IIIa receptor antagonist use					
FRISC-II	141/1222	195/1235		66.2 %	0.73 [0.60, 0.89]
RITA-3	46/895	57/915		18.9 %	0.83 [0.57, 1.20]
Subtotal (95% CI)	**2117**	**2150**		**85.2 %**	**0.75 [0.63, 0.90]**
Total events: 187 (Invasive), 252 (Conservative)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.31, df = 1 (P = 0.58); I^2 =0.0%					
Test for overall effect: Z = 3.16 (P = 0.0016)					
Total (95% CI)	**2721**	**2746**		**100.0 %**	**0.78 [0.67, 0.92]**
Total events: 227 (Invasive), 291 (Conservative)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.92, df = 2 (P = 0.38); I^2 =0.0%					
Test for overall effect: Z = 2.89 (P = 0.0038)					

Analysis 1.9. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 9 Index Death or Non-Fatal MI.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 9 Index Death or Non-Fatal MI



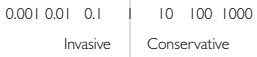
Analysis 1.10. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 10 Early Death or Non-Fatal MI.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 10 Early Death or Non-Fatal MI

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Routine glycoprotein IIb/IIIa receptor antagonist use					
TACTICS-TIMI 18	52/1114	77/1106		94.6 %	0.67 [0.48, 0.94]
Subtotal (95% CI)	**1114**	**1106**		**94.6 %**	**0.67 [0.48, 0.94]**
Total events: 52 (Invasive), 77 (Conservative)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.29 (P = 0.022)					
2 No routine glycoprotein IIb/IIIa receptor antagonist use					
VINO	2/64	7/67		5.4 %	0.30 [0.06, 1.39]
Subtotal (95% CI)	**64**	**67**		**5.4 %**	**0.30 [0.06, 1.39]**
Total events: 2 (Invasive), 7 (Conservative)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.54 (P = 0.12)					
Total (95% CI)	**1178**	**1173**		**100.0 %**	**0.64 [0.45, 0.92]**
Total events: 54 (Invasive), 84 (Conservative)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 1.02, df = 1 (P = 0.31); I^2 =2%					
Test for overall effect: Z = 2.42 (P = 0.015)					



Analysis 1.11. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 11 Intermediate Death or Non-Fatal MI.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 11 Intermediate Death or Non-Fatal MI

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Routine glycoprotein IIb/IIIa receptor antagonist use					
TACTICS-TIMI 18	81/1114	105/1106		30.6 %	0.77 [0.58, 1.01]
Subtotal (95% CI)	**1114**	**1106**		**30.6 %**	**0.77 [0.58, 1.01]**
Total events: 81 (Invasive), 105 (Conservative)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.88 (P = 0.060)					
2 No routine glycoprotein IIb/IIIa receptor antagonist use					
FRISC-II	127/1222	174/1235		39.1 %	0.74 [0.60, 0.91]
RITA-3	68/895	76/915		26.6 %	0.91 [0.67, 1.25]
VINO	4/64	15/67		3.7 %	0.28 [0.10, 0.80]
Subtotal (95% CI)	**2181**	**2217**		**69.4 %**	**0.74 [0.52, 1.04]**
Total events: 199 (Invasive), 265 (Conservative)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 4.91, df = 2 (P = 0.09); I^2 =59%					
Test for overall effect: Z = 1.74 (P = 0.082)					
Total (95% CI)	**3295**	**3323**		**100.0 %**	**0.76 [0.62, 0.94]**
Total events: 280 (Invasive), 370 (Conservative)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 4.91, df = 3 (P = 0.18); I^2 =39%					
Test for overall effect: Z = 2.56 (P = 0.011)					

Analysis 1.12. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 12 Intermediate Death or Non-Fatal MI; Gender Sub-Analysis.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 12 Intermediate Death or Non-Fatal MI; Gender Sub-Analysis

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Male					
FRISC-II	84/872	132/834		24.9 %	0.61 [0.47, 0.79]
RITA-3	38/545	59/583		17.1 %	0.69 [0.47, 1.02]
TACTICS-TIMI 18	55/719	70/744		19.9 %	0.81 [0.58, 1.14]
Subtotal (95% CI)	**2136**	**2161**		**61.9 %**	**0.68 [0.57, 0.81]**
Total events: 177 (Invasive), 261 (Conservative)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.80$, df = 2 (P = 0.41); $I^2 = 0.0\%$					
Test for overall effect: Z = 4.19 (P = 0.000028)					
2 Female					
FRISC-II	36/344	33/398		14.5 %	1.26 [0.80, 1.98]
RITA-3	17/350	30/332		10.4 %	0.54 [0.30, 0.96]
TACTICS-TIMI 18	26/395	35/362		13.2 %	0.68 [0.42, 1.11]
Subtotal (95% CI)	**1089**	**1092**		**38.1 %**	**0.79 [0.48, 1.31]**
Total events: 79 (Invasive), 98 (Conservative)					
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 6.16$, df = 2 (P = 0.05); $I^2 = 68\%$					
Test for overall effect: Z = 0.91 (P = 0.36)					
Total (95% CI)	**3225**	**3253**		**100.0 %**	**0.73 [0.59, 0.91]**
Total events: 256 (Invasive), 359 (Conservative)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 9.22$, df = 5 (P = 0.10); $I^2 = 46\%$					
Test for overall effect: Z = 2.78 (P = 0.0055)					

Analysis 1.13. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 13 Late Death or Non-Fatal MI.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 13 Late Death or Non-Fatal MI

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Routine glycoprotein IIb/IIIa receptor antagonist use					
ICTUS	76/604	63/596		23.0 %	1.19 [0.87, 1.63]
Subtotal (95% CI)	**604**	**596**		**23.0 %**	**1.19 [0.87, 1.63]**
Total events: 76 (Invasive), 63 (Conservative)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.09 (P = 0.28)					
2 No routine glycoprotein IIb/IIIa receptor antagonist use					
FRISC-II	217/1222	270/1235		41.3 %	0.81 [0.69, 0.95]
RITA-3	142/895	178/915		35.7 %	0.82 [0.67, 1.00]
Subtotal (95% CI)	**2117**	**2150**		**77.0 %**	**0.81 [0.72, 0.92]**
Total events: 359 (Invasive), 448 (Conservative)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 3.23 (P = 0.0012)					
Total (95% CI)	**2721**	**2746**		**100.0 %**	**0.89 [0.73, 1.08]**
Total events: 435 (Invasive), 511 (Conservative)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 4.87, df = 2 (P = 0.09); I^2 =59%					
Test for overall effect: Z = 1.20 (P = 0.23)					

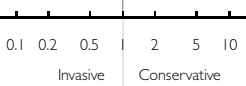
Analysis 1.14. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 14 Intermediate Refractory Angina.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 14 Intermediate Refractory Angina

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Routine glycoprotein IIb/IIIa receptor antagonist use					
ICTUS	85/604	77/596		20.1 %	1.09 [0.82, 1.45]
TACTICS-TIMI 18	430/1114	660/1106		31.4 %	0.65 [0.59, 0.71]
Subtotal (95% CI)	**1718**	**1702**		**51.6 %**	**0.82 [0.49, 1.38]**
Total events: 515 (Invasive), 737 (Conservative)					
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 11.89$, df = 1 (P = 0.00057); $I^2 = 92\%$					
Test for overall effect: Z = 0.73 (P = 0.46)					
2 No routine glycoprotein IIb/IIIa receptor antagonist use					
FRISC-II	256/1222	455/1235		29.4 %	0.57 [0.50, 0.65]
RITA-3	58/895	106/915		19.1 %	0.56 [0.41, 0.76]
Subtotal (95% CI)	**2117**	**2150**		**48.4 %**	**0.57 [0.50, 0.64]**
Total events: 314 (Invasive), 561 (Conservative)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.92); $I^2 = 0.0\%$					
Test for overall effect: Z = 9.22 (P < 0.00001)					
Total (95% CI)	**3835**	**3852**		**100.0 %**	**0.67 [0.55, 0.83]**
Total events: 829 (Invasive), 1298 (Conservative)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 17.12$, df = 3 (P = 0.00067); $I^2 = 82\%$					
Test for overall effect: Z = 3.80 (P = 0.00014)					



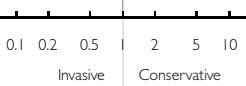
Analysis 1.15. Comparison 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use, Outcome 15 Intermediate Rehospitalization.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 1 All studies undertaken in the stent era regardless of glycoprotein IIb/IIIa receptor use

Outcome: 15 Intermediate Rehospitalization

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Routine glycoprotein IIb/IIIa receptor antagonist use					
ICTUS	44/604	64/596		6.8 %	0.68 [0.47, 0.98]
TACTICS-TIMI 18	123/1114	152/1106		17.3 %	0.80 [0.64, 1.00]
Subtotal (95% CI)	**1718**	**1702**		**24.1 %**	**0.77 [0.63, 0.93]**
Total events: 167 (Invasive), 216 (Conservative)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.60$, df = 1 (P = 0.44); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.72 (P = 0.0065)					
2 No routine glycoprotein IIb/IIIa receptor antagonist use					
FRISC-II	451/1222	704/1235		75.3 %	0.65 [0.59, 0.71]
VINO	4/64	6/67		0.6 %	0.70 [0.21, 2.36]
Subtotal (95% CI)	**1286**	**1302**		**75.9 %**	**0.65 [0.59, 0.71]**
Total events: 455 (Invasive), 710 (Conservative)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.90); $I^2 = 0.0\%$					
Test for overall effect: Z = 9.71 (P < 0.00001)					
Total (95% CI)	**3004**	**3004**		**100.0 %**	**0.67 [0.61, 0.74]**
Total events: 622 (Invasive), 926 (Conservative)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.23$, df = 3 (P = 0.36); $I^2 = 7\%$					
Test for overall effect: Z = 7.95 (P < 0.00001)					



Analysis 2.1. Comparison 2 Safety end-points, Outcome 1 Procedure-related MI.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 2 Safety end-points

Outcome: 1 Procedure-related MI

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
FRISC-II	66/1222	36/1235		45.3 %	1.85 [1.24, 2.76]
ICTUS	72/604	36/596		48.8 %	1.97 [1.34, 2.90]
RITA-3	15/895	4/915		5.9 %	3.83 [1.28, 11.51]
Total (95% CI)	**2721**	**2746**		**100.0 %**	**2.00 [1.53, 2.61]**

Total events: 153 (Invasive), 76 (Conservative)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.50$, df = 2 (P = 0.47); $I^2 = 0.0\%$

Test for overall effect: Z = 5.05 (P < 0.00001)

Analysis 2.2. Comparison 2 Safety end-points, Outcome 2 Bleeding.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 2 Safety end-points

Outcome: 2 Bleeding

Study or subgroup	Invasive n/N	Conservative n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
FRISC-II	112/1222	81/1235		41.3 %	1.40 [1.06, 1.84]
RITA-3	73/895	32/915		29.3 %	2.33 [1.56, 3.50]
TACTICS-TIMI 18	61/1114	36/1106		29.4 %	1.68 [1.12, 2.52]
Total (95% CI)	**3231**	**3256**		**100.0 %**	**1.71 [1.27, 2.31]**

Total events: 246 (Invasive), 149 (Conservative)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 4.22$, df = 2 (P = 0.12); $I^2 = 53\%$

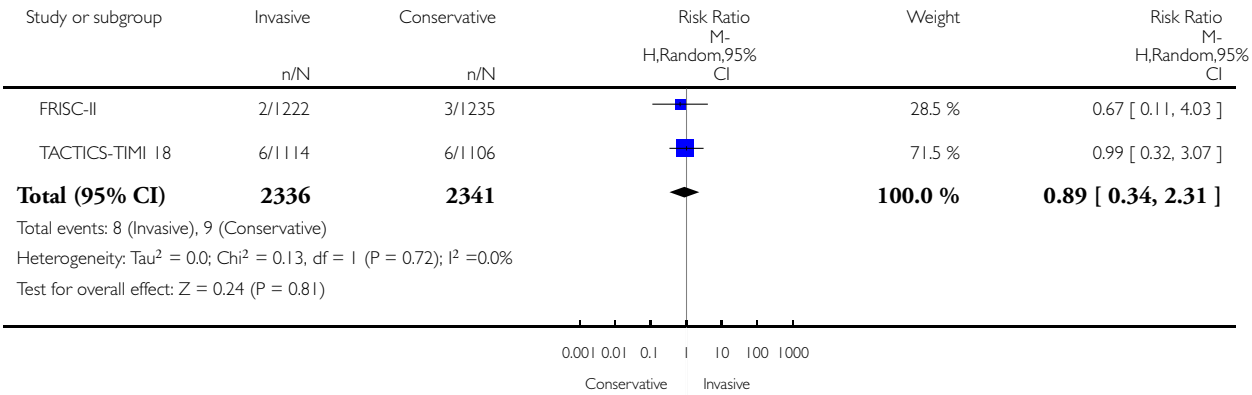
Test for overall effect: Z = 3.53 (P = 0.00042)

Analysis 2.3. Comparison 2 Safety end-points, Outcome 3 Stroke.

Review: Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era

Comparison: 2 Safety end-points

Outcome: 3 Stroke



ADDITIONAL TABLES

Table 1. Detailed characteristics of included studies, rates of angiography and revasculization

Study Characteristic	TACTICS-TIMI 18	ICTUS	RITA-3	FRISC-II	VINO
Year of publication	2001	2005	2002	1999	2001
Total Number of Patients	2220	1200	1810	2457	131
Stent use in invasive arm %	83	88	88	61	47
Men %	66	74	62	70	80
Mean Age	62	62	63	65	66

Table 1. Detailed characteristics of included studies, rates of angiography and revasculization (*Continued*)

Trial Duration	6 months	4 years	5 years	5 years	6 months
Diabetes mellitus %	28	14	13	13	25
Myocardial Infarction on trial enrolment %	54	100	75	58	100
Previous myocardial infarction %	29	23	28	23	26
ST depression %	39	48	37	46	47
Mortality in conservatively managed patients at end of follow up % (note different trial durations)	3.5	7.7	14	10.1	13.4
Mortality in conservatively managed patients expressed as an average mortality per year of follow up %/year	7.0	1.9	2.8	2.0	26.8
Myocardial Infarction rate in conservatively managed patients at end of follow up % (note different trial durations)	6.9	12.3 (as per trial definition)	6.2	17.7	14.9
Glycoprotein 2b/3a receptor antagonist use in invasive arm %	94	94	9	10	0
Revascularization at end of follow up invasive/conservative %	61/44	81/58	61/38	80/52	78/39
Difference in revascularization rates at end of follow up between the 2 strate-	17	23	23	28	39

Table 1. Detailed characteristics of included studies, rates of angiography and revasculization (*Continued*)

gies %					
Percentage of revascularization procedures in the invasive group being CABG %	22	24	42	41	35
Medical Co-Interventions (% of patients enrolled)	aspirin: 98; unfractionated heparin: 99; beta-blocker: 82; statin: 52; clopidogrel: 0 (this was a criterion for exclusion)	aspirin: 100 as per protocol, enoxaparin: 100 as per protocol, statin: 92, clopidogrel: 55	aspirin: 92; enaxaparin: 84; unfractionated heparin: 11; beta-blocker: 72; calcium channel antagonist: 35; ACE inhibitor: 18; statin: 45	aspirin: 93; dalteparin 50; unfractionated heparin: 50; beta-blocker: 79; calcium channel antagonist: 20; statin: 56	aspirin: 100 as per protocol, heparin: 100 as per protocol; beta-blocker: 76; calcium channel antagonist: 9; ACE inhibitor: 47; statin: 43

Table 2. Definitions of myocardial infarction in the included studies

Study Name	Definition for Non-Procedural Myocardial Infarction	Definition of Procedural Myocardial Infarction	More than one definition of Myocardial Infarction?	Definition of Myocardial Infarction Used in this Review
RITA-3	Clinical symptoms, ECG changes and CK-MB or Toponin >2 x upper limit of normal greater than 24 hours post-randomization	Clinical symptoms, ECG changes and CK-MB or Toponin >2 x upper limit of normal greater than 24 hours post-randomization	Yes	As per trial definition
ICTUS	CK-MB > upper limit of normal or a 50% decline from a peak value followed by subsequent rise to a value greater than the upper limit of normal. An increased troponin above the upper limit of normal was also used beyond one year of follow up	CK-MB > upper limit of normal or a 50% decline from a peak value followed by subsequent rise to a value greater than the upper limit of normal. New Q waves on the electrocardiogram were used to define myocardial infarction associated with coronary artery bypass grafting	Yes	In various publications, the investigators report the myocardial infarction end point as 1. total myocardial infarction 2. spontaneous myocardial infarction and 3. procedural myocardial infarction. We utilized spontaneous myocardial infarction for our myocardial infarction end-point, death/spontaneous myocardial infarction for our death or myocardial infarction composite and procedural my-

Table 2. Definitions of myocardial infarction in the included studies (*Continued*)

				ocardial infarction is reported as a safety end point. Since the prognostic value of peri-procedural infarctions is still debated, 'spontaneous' myocardial infarction is our preferred end point since this allows for consistency with the other trials
TACTIC TIMI 18	CK-MB > upper limit of normal or >50% over previous	CK-MB > 3 times upper limit of normal or >50% over previous	No	As per trial definition
VINO	Recurrent ischemic chest pain lasting >20 minutes, new ECG changes and CK-MB > 1.5 times the upper limit of normal after 72 hours post-randomization	Recurrent ischemic chest pain lasting >20 minutes, new ECG changes and CK-MB > 1.5 times the upper limit of normal after 72 hours post-randomization	No	As per trial definition
FRISC-II	Two or three of the following criteria: chest pain, ECG changes or elevated markers of myocardial damange. Marker definitions: CK-MB mass > upper limit of normal or CK, CK-B, CK-MB activity > 2 times upper limit of normal in 1 sample of CK-MB activity > upper limit of normal in 2 samples	Two or three of the following criteria: chest pain, ECG changes or elevated markers of myocardial damange. Marker definitions: CK-MB mass > 1.5 times upper limit of normal or CK, CK-B, CK-MB activity > 3 times upper limit of normal in 1 sample of CK-MB activity > 2 times upper limit of normal in 2 samples	No	As per trial definition

APPENDICES

Appendix 1. Search strategies

CENTRAL on The Cochrane Library

#1 MeSH descriptor Angina, Unstable explode all trees
#2 unstable next angina in All Text
#3 coronary next syndrome* in All Text
#4 MeSH descriptor Myocardial Infarction explode all trees
#5 myocardial next infarct* in All Text
#6 heart next infarct* in All Text
#7 nstemi in All Text
#8 unstable next coronary in All Text
#9 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)
#10 (ischaemi* in All Text near/6 guid* in All Text)
#11 (ischemi* in All Text near/6 guid* in All Text)
#12 (early in All Text near/6 invasive in All Text)
#13 (invasive in All Text near/6 conservative in All Text)
#14 (angiography in All Text near/6 invasive in All Text)
#15 (angiography in All Text near/6 conservative in All Text)
#16 (ischemi* in All Text near/6 strateg* in All Text)
#17 (ischaemi* in All Text near/6 strateg* in All Text)
#18 (conservative in All Text near/6 strateg* in All Text)
#19 (conservative in All Text near/6 therap* in All Text)
#20 (conservative in All Text near/6 treatment* in All Text)
#21 (conservative in All Text near/6 management in All Text)
#22 (interventional in All Text near/6 strateg* in All Text)
#23 (interventional in All Text near/6 therap* in All Text)
#24 (interventional in All Text near/6 treatment* in All Text)
#25 (interventional in All Text near/6 management in All Text)
#26 (invasive in All Text near/6 strateg* in All Text)
#27 (invasive in All Text near/6 therap* in All Text)
#28 (invasive in All Text near/6 treatment* in All Text)
#29 (invasive in All Text near/6 management in All Text)
#30 (triage in All Text near/6 angiograph* in All Text)
#31 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19)
#32 (#20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
#33 (#31 or #32)
#34 (#9 and #33)

MEDLINE (on Ovid)

1 Myocardial Infarction/
2 exp Angina, Unstable/
3 Acute Coronary Syndrome/
4 unstable angina$.tw.
5 coronary syndrome$.tw.
6 myocardial infarction$.tw.
7 or/1-6
8 (intervention$ adj2 (strateg$ or therapy or therapies or treatment$)).tw.
9 (conservative adj2 (strateg$ or therapy or therapies or treatment$)).tw.

10 (invasive adj2 (strateg$ or therapy or therapies or treatment$)).tw.
11 8 or 9 or 10
12 7 and 11 (
13 (isch?emia adj2 guide$).tw.
14 ((invasive or conservative) adj2 management).tw.
15 11 or 13 or 14
16 7 and 15
17 randomized controlled trial.pt.
18 controlled clinical trial.pt.
19 Randomized controlled trials/
20 random allocation/
21 double blind method/
22 single-blind method/
23 or/17-22
24 exp animal/ not humans/
25 23 not 24
26 clinical trial.pt.
27 exp Clinical Trials as Topic/
28 (clin$ adj25 trial$).ti,ab.
29 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
30 placebos/
31 placebo$.ti,ab.
32 random$.ti,ab.
33 research design/
34 or/26-33
35 34 not 24
36 35 not 25
37 comparative study.pt.
38 exp evaluation studies/
39 follow up studies/
40 prospective studies/
41 (control$ or prospectiv$ or volunteer$).ti,ab.
42 or/37-41
43 42 not 24
44 43 not (25 or 36)
45 25 or 36 or 44
46 45 and 16

EMBASE (on Ovid)

1 exp heart infarction/
2 exp unstable angina pectoris/
3 Acute Coronary Syndrome/
4 unstable angina$.tw.
5 coronary syndrome$.tw.
6 myocardial infarct$.tw.
7 heart infarct$.tw.
8 nstemi.tw.
9 unstable coronary.tw.
10 or/1-8
11 (isch?emi$ adj3 guid$).tw.
12 (early adj3 invasive$).tw.
13 (early adj3 conservative$).tw.

14 (isch?emi$ adj3 strateg$).tw.
15 (conservative adj3 (strateg$ or therapy or therapies or treatment$ or management)).tw.
16 (interventional adj3 (strateg$ or therapy or therapies or treatment$ or management)).tw.
17 (invasive adj3 (strateg$ or therap$ or treatment$ or management)).tw.
18 (triage adj3 angiograph$).tw.
19 or/11-18
20 10 and 19
21 controlled study/
22 clinical trial/
23 major clinical study/
24 random$.tw.
25 randomized controlled trial/
26 trial$.tw.
27 compar$.tw.
28 control$.tw.
29 follow-up.tw.
30 blind$.tw.
31 double blind procedure/
32 placebo$.tw.
33 clinical article/
34 placebo/
35 doubl$.tw.
36 or/21-35
37 20 and 36
38 limit 37 to yr="1996 - 2008"

MEDLINE (Ovid) search for 2006 version of the review

#1 explode 'Myocardial-Infarction' /
#2 explode 'Angina-Unstable' /
#3 unstable angina$
#4 coronary syndrome$
#5 myocardial infarct$
#6 myocardial infarction heart infarct$
#7 nstemi
#8 unstable coronary
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 ischaemi$ adj3 guid$
#11 ischemi$ adj3 guid$
#12 early adj3 invasive
#13 invasive adj3 conservative
#14 ischemi$ adj3 strateg$
#15 ischaemi$ adj3 strateg$
#16 conservative adj3 strateg$
#17 conservative adj3 therap$
#18 conservative adj3 treatment$
#19 conservative adj3 management
#20 interventional adj3 strateg$
#21 interventional adj3 therap$
#22 interventional adj3 treatment$
#23 interventional adj3 management
#24 invasive adj3 strateg$
#25 invasive adj3 therap$

#26 invasive adj3 treatment$
#27 invasive adj3 management
#28 triage adj3 angiograph$
#29 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28
#30 #9 and #29
A randomized controlled trial filter was used as described in the Cochrane Handbook.

WHAT'S NEW

Last assessed as up-to-date: 13 August 2008.

Date	Event	Description
27 February 2009	New search has been performed	The search was updated to February 2008. Twenty-two additional potentially relevant references were identified. Five references reporting on two studies were subsequently excluded. The remaining 14 references were additional reports of already included studies. Long-term follow-up data from the ICTUS trial have been added
27 February 2009	New citation required but conclusions have not changed	Change of authors.

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 3, 2006

Date	Event	Description
27 October 2008	Amended	Converted to new review format.
5 March 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

MRH is the primary author of the review. He was involved in writing and designing the review and in data extraction and analysis.

CNA provided advice regarding inclusion criteria and the clinical end-points.

IAS assisted in the drafting of the research question, providing background literature, and in reviewing protocol methods.

DECLARATIONS OF INTEREST

CN Aroney has received travel grants from Boston Scientific, J&J, Medtronic, MSD, Eli Lilly.

INDEX TERMS

Medical Subject Headings (MeSH)

*Angioplasty, Balloon, Coronary [adverse effects]; *Stents; Angina, Unstable [mortality; surgery; *therapy]; Coronary Angiography; Coronary Artery Disease [therapy]; Myocardial Infarction [mortality; surgery; *therapy]; Platelet Glycoprotein GPIIb-IIIa Complex [antagonists & inhibitors]; Randomized Controlled Trials as Topic; Sex Factors

MeSH check words

Female; Humans; Male