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

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[Intervention Review]

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

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ABSTRACT

Background

In patients with unstable angina and non-ST-elevation myocardial infarction (UA/NSTEMI) two strategies are possible: 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 a conservative strategy for treating UA/NSTEMI in the stent era.

Search strategy

The Cochrane Central Register of Controlled Trials (Issue 3 2005), MEDLINE and EMBASE were searched from 1996 to September 2005 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 5 studies (7818 participants). Using intention-to-treat analysis with random effects models, summary estimates of relative risk (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-square and variance (I^2) methods.

Main results

In the all-study analysis, mortality during initial hospitalization showed a trend to hazard with an invasive strategy; relative risk 1.59 (95% CI 0.96 to 2.64). Mortality and myocardial infarction assessed at 2-5 years in two trials were significantly decreased by an invasive strategy with relative risk of 0.75 (95% CI 0.62 to 0.92) and 0.75 (95% CI 0.61 to 0.91) respectively. The composite endpoint of death or non-fatal myocardial infarction was significantly decreased by an invasive strategy at several time points after initial hospitalization. The incidence of early (<4 months) and intermediate (6-12 months) refractory angina were both significantly decreased by an invasive strategy; relative risk 0.47 (95% CI 0.32 to 0.68) and 0.67 (95% CI 0.55 to 0.83) respectively, as were early and intermediate rehospitalization rates with relative risk 0.60 (95% CI 0.41 to 0.88) and 0.67 (95% CI 0.61 to 0.74) respectively. The invasive strategy was associated with a two-fold increase in the relative risk of peri-procedural myocardial infarction (as variably defined) and a 1.7-fold increase in the relative risk of bleeding.

Authors' conclusions

An early invasive strategy is preferable to a conservative strategy in the treatment of UA/NSTEMI.

PLAIN LANGUAGE SUMMARY

Should all patients with unstable angina and non-ST elevation myocardial infarction be subjected to an invasive strategy comprising coronary angiography and, if indicated, percutaneous coronary intervention, within 48 hours of admission?

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 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 to look for atherosclerotic narrowing. If a significant narrowing or complicated plaque is found then it may be dilated by means of a balloon catheter being inserted and inflated across the narrowing, and patency of the vessel 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 strategy, the conservative strategy, patients are initially treated with drugs and only patients who suffer more chest pain while receiving 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 two studies suggests that it reduces the risk of dying and the risk of having another heart attack by one quarter two to five years following the event. Based on review of all available studies, the invasive strategy is preferable.

BACKGROUND

The diagnosis of acute coronary syndromes

The acute coronary syndromes (ACS) encompass three disorders of related etiology: 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: 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 on pre-existing plaque, i.e. acute plaque change, is the most common. Indeed, the majority of patients with ACS have 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 1 year mortality rate (Armstrong 1998). UA/NSTEMI is much more common than STEMI; in the United States, 1.3 million patients were admitted to hospital with UA/NSTEMI compared to 350,000 with STEMI (AHA 1999). Whereas emergency percutaneous coronary revascularization is now a commonly used therapy for treating STEMI (Cucherat 2003; Antman 2004), 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 will be 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 ACC/AHA guidelines (Braunwald 2002) fall into two major groups: anti-ischemic therapies and anti-platelet/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/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 ACE inhibitors has been shown to be beneficial in myocardial infarction (EUROPA 2003; HOPE 2000; Rodrigues 2003). Of the anti-platelet/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, has also been shown to be beneficial in UA/NSTEMI (Gurfinkel 1995; 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 patient's 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 e.g. recurrent infarction, angina at rest, dynamic ST changes on 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 disease may be discharged and the need for readmission for recurrent pain is virtually eliminated. Those with coronary disease on angiography can be treated expeditiously according to their angiography 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 them 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 will vary depending on a number of factors: clinical expertise (Singh 2000); volume of procedures undertaken (Magid 2000); and methods and protocols used, especially in regards to pharmacological and procedural co-interventions. Of particular importance in contemporary practice are the use of glycoprotein IIb/IIIa receptor antagonists (CAPTURE 1997; EPIC 1994; EPILOG 1997; EPISTENT 1998; Karvouni 2003), and use of coronary artery stents (Al Suwaidi 2004), both of which have been shown to improve outcomes and reduce complications when used with invasive procedures. A recent publication by the TIMI study group highlights 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, the more recent TACTICS-TIMI 18 study used pre-procedural (upstream) glycoprotein IIb/IIIa receptor antagonists and stents as standard treatment. Importantly, this paper showed that after adjustment for baseline risk, an early invasive strategy tended to more favorable results in TACTICS-TIMI 18 than in TIMI-3b. Consequently, in this review, only studies undertaken in the stent era were considered for inclusion. Stenting as 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. If non-stent studies were to be included, the analysis would under-estimate the benefits of an early invasive strategy on endpoints such as recurrent angina and rehospitalization (e.g. due to chest pain). After meeting this review's requirement of routine stent use, the included studies were also stratified in further analyses by the adjunctive use of glycoprotein IIb/IIIa receptor antagonists during PCI.

OBJECTIVES

The objectives of this review are two fold:

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

(2) To determine the benefits and harms of 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

Studies for inclusion in this review were randomized controlled clinical trials comparing invasive and conservative strategies in patients with UA/NSTEMI in which at least one of this review's outcomes was measured. Revascularization approaches in included studies must consist of PCI or CABG as required. Stents must 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 further 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 via PCI regardless of glycoprotein IIb/IIIa receptor antagonist use;
Analysis 2: Stents and glycoprotein IIb/IIIa receptor antagonists deployed routinely in revascularization procedures via PCI;
Analysis 3: Stents but not glycoprotein IIb/IIIa receptor antagonists deployed routinely in revascularization procedures via PCI.

Types of participants

Included studies recruited men and women who were at least 18 years old who had an episode of angina with an accelerating pattern or 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 2 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 compared are:
(1) routine invasive: routine angiography ±revascularization in all patients; this is carried out in all eligible patients unless they have contraindications to angiography;
(2) conservative: angiography ±revascularization only in eligible patients with evidence of cardiac ischemia e.g. recurrent ischemia, dynamic ECG changes or a positive stress test.
Revascularization modalities include 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 measures
(1) Death: all causes

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

Secondary measures
(1) Rehospitalization for acute coronary syndromes
(2) Complications of angiography/revascularization i.e. bleeding, procedure-related mortality or myocardial infarction
Differentiating peri-PCI enzyme leaks from the outcome measure of non-fatal myocardial infarction warrants further comment. The ACC/AHA defines peri-PCI myocardial infarction by either an elevation in cardiac enzymes or by electrocardiographic criteria. However, not all included studies involved the routine measurement of cardiac enzymes following PCI. Procedural myocardial infarction was reported as a safety end point where data were available.

Prespecified Subgroup Analyses:
For the primary end-point of all-cause death or non-fatal myocardial infarction, the following subgroup analyses were undertaken where data were available:

- gender;
- troponin status;
- ST-depression on admission;
- TIMI risk score [0-2, 3-4, 5-7] (Antman 2000).

Search methods for identification of studies

The databases searched included: The Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library (Issue 3 2005), MEDLINE (1996 to September 2005) and EMBASE (1996 to September 2005). No language restrictions were applied. The restriction of 1996 onwards was applied because of low rates of stent use prior to that year. The strategy for MEDLINE is described below:
#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 clinical trial filter was used as described in the Cochrane Handbook.
Further, reference lists of retrieved articles were searched and experts in the field contacted for additional information.

Data collection and analysis

Study selection
Two reviewers (MRH, JAD) selected articles independently for inclusion in the review. A study was considered eligible for inclusion if it was a prospective trial that compared the routine invasive with the conservative strategy in patients with UA/NSTEMI. Specific exclusion criteria are mentioned in the TYPES OF STUDIES section above. Disagreement was resolved first by consensus and then by consultation with content experts (CNA, IAS).

Data extraction
Data were extracted independently by two reviewers (MRH, JAD) on data extraction sheets. Disagreement was resolved first by consensus and then by consultation with content experts (CNA, IAS).

Quality assessment
All included studies were assessed independently by two reviewers for quality. Please refer to the Table 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 its conclusion? Were the conclusions reached by intention to treat analysis?

Statistical considerations
Data were analyzed 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 and the 95% confidence interval. Heterogeneity was statistically assessed using the chi-square test ($p<0.10$) for all end points and the I^2 statistic (Higgins 2003) for selected end points. The I^2 statistic is displayed on the forest plots for all analyses.

As stated under the heading "types of studies", all included studies were further analyzed by assignment to one of two analyses depending on the routine use of glycoprotein IIb/IIIa receptor antagonists. We compared the invasive versus the conservative strategy within each analysis.

RESULTS

Description of studies

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

The literature search yielded 12 studies that were considered for this review. 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). Three 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; VANQWISH 1998). As was already stated, such studies 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 table of excluded studies . Five studies were deemed appropriate for inclusion and are described in the table of included studies. These five studies are analyzed together in analysis 1. Two of these studies used a glycoprotein IIb/IIIa antagonist routinely in the invasive arm; TACTICS-TIMI 18 and ICTUS. These two studies were analyzed 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 and were analyzed together as analysis 3 (FRISC-II; RITA-3; VINO 2002). 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 loss 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 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 can 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/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:

The interventions compared comprise the invasive or conservative treatment strategies. In the invasive strategy, all patients were randomized to receive angiography regardless of symptomatic status whereas in the conservative strategy angiography was only performed in patients with clinical or investigational evidence of ischemia. Evidence clearly shows that patients with recurrent ischemia who do not have angiography have worse outcomes (TRUCS 2000). It is important to note that angiography is a component of both strategies and that angiography in the conservative arm does 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 2 days in RITA-3 and mean 4 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 6 hours of randomization) to "delayed invasive" (angiography in 3-5 days) in UA/NSTEMI patients and found that early angiography produced superior outcomes to delayed angiography. This finding needs to be replicated in further prospective trials and possibly incorporated into future trials in UA/NSTEMI. 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 would mandate 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 proved 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 and/or ECG 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. Since ICTUS and TACTICS-TIMI 18 both employed routine glycoprotein IIb/IIIa receptor antagonists with PCI and are analyzed together in analysis 2, the TACTICS-TIMI 18 definition of myocardial infarction was applied to the ICTUS data in analyzing this outcome for consistency across studies. In conclusion, the clinical trials differed in their definitions of myocardial infarction and this should be taken into account when interpreting the findings of this analysis. Fortunately, end points such as death are indisputable. Follow up was 6 months in TACTICS-TIMI 18 & VINO, 12 months in ICTUS, 24 months in FRISC-II and 5 years in RITA-3; characteristics of the included studies are summarized in the table 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 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 analyzed together in analysis 2 since they both involved the routine use of both glycoprotein IIb/IIIa receptor antagonists and stents. Analysis 3 included studies that used only stenting routinely and includes 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 4 months. "Intermediate" end points indicate a follow up greater than or equal to 6 months or less than or equal to 12 months. "Late" end points indicate a follow up greater than or equal to 2 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 6 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 2002

Death (Index, Early, Intermediate):

Index death showed a trend to hazard with the early invasive strategy having a relative risk of 1.59 (95% confidence interval 0.96 to 2.64). Early and intermediate death were not improved by an invasive strategy although late death as reported in FRISC-II and RITA-3 data was significantly decreased; relative risk 0.75 (95% confidence interval 0.62 to 0.92). Significant heterogeneity (p= 0.09) was detected in the analysis of intermediate death which is the only analysis that included data from all 5 included studies. The I^2 statistic for the intermediate death analysis was 51% which indicates that the finding of heterogeneity cannot be assumed to be due to chance.

Some of the heterogeneity at the intermediate (6-12 month) time point may be explained by differences between trials in death rates standardized to years of study duration shown in Table 02. The rates were 2.5-2.8% 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 are 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 6 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.

Another important finding of this analysis was that mortality benefits only become apparent after long term (2-5 year) follow up. The importance of this observation is that over time, deaths accrue and increase the power of a given study to find a significant mortality difference. This 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 are those that randomized the highest risk patients (VINO) and those that had the longest follow up (RITA-3). Hence, it may be inappropriate to simply consider outcomes at one time point e.g. 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. The finding of long term benefit is particularly interesting since the mortality benefit of CABG over medical therapy for stable angina only emerges after 3 years and following an early hazard for surgery (Yusuf 1994).

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 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 6 or 12 months. There was no benefit for the early invasive strategy although heterogeneity (p=0.02) was found, driven by the results of ICTUS. The I^2 statistic for the intermediate myocardial infarction analysis was 66%, indicating that observed heterogeneity was not due to chance. This is not a surprising finding considering the different definitions of myocardial infarction in the included studies (Table 2) and specifically, the routine measurement of cardiac biomarkers after intervention in ICTUS and the inclusion of these peri-PCI leaks in the myocardial infarction end point. Late myocardial infarction, based on 2 year FRISC-II data and 5 year RITA-3 data, was significantly decreased by the invasive strategy; relative risk 0.75 (95% confidence interval 0.61 to 0.91).

Death or Non-Fatal Myocardial Infarction (Index, Early, Intermediate, Late):

The ICTUS investigators did not report this end point and the components of the composite have been analyzed individually and have shown significant heterogeneity. 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. 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 relative risk of 0.64 (95% confidence interval 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; relative risk 0.76 (95% confidence interval 0.62 to 0.94). No significant heterogeneity was found. Late death or non-fatal myocardial infarction was also significantly decreased; however both components of this composite achieved statistical significance independently as already described. Combining data for subgroup analysis was not possible because TACTICS-TIMI 18 dichotomized patients at TnT of 0.01 ng/ml and TnI of 0.1 ng/ml whereas FRISC-II presented data based on TnT levels of 0.1 ng/ml or 0.3 ng/ml. Gender sub-analysis for intermediate death or non-fatal myocardial infarction showed that the benefit of the invasive strategy only reached statistical significance in males; relative risk of 0.68 (95% confidence interval 0.57 to 0.81). Interestingly, the data for women showed significant heterogeneity between the 3 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; relative risk 0.52 (95% confidence interval 0.36 to 0.75). However, the confidence interval in the female subgroup was wide and overlapped with that of their male counterparts. This is likely due to the small number of females in the included studies.

Refractory Angina (Early, Intermediate):

An invasive strategy decreased early refractory angina based on 4 month data from RITA-3; relative risk 0.47 (95% confidence interval 0.32 to 0.68). Intermediate refractory angina was significantly decreased by an early invasive strategy with a relative risk of 0.67 (95% confidence interval 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 is 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 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):

The invasive strategy was associated with an early relative risk of 0.60 (95% confidence interval 0.41 to 0.88) and an intermediate relative risk of 0.67 (95% confidence interval 0.61 to 0.74).

Analysis 2: Routine use of both stents and glycoprotein IIb/IIIa receptor antagonists. TACTICS-TIMI 18 and ICTUS

This analysis included trials that are as close as possible to an "ideal" invasive strategy; i.e. a strategy that involved the routine use of both glycoprotein IIb/IIIa receptor antagonists and stents. Unfortunately, the ICTUS trial only reported outcomes at 1 year and did not include the composite end point of death or non-fatal myocardial infarction. Hence, much of the data regarding early follow up is based solely on the results of TACTICS-TIMI 18.

Death (Index, Early, Intermediate):

There was no difference between the treatment strategies at any of the time points assessed. Data from TACTICS-TIMI 18 suggest a trend to 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 6 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.

Myocardial Infarction (Index, Early, Intermediate)

Based on TACTIC-TIMI 18 data, the invasive strategy was associated with a relative risk of 0.61 (95% confidence interval 0.38 to 0.98) at index hospitalization. Hence, there does not appear to be an early hazard to an invasive strategy when glycoprotein IIb/IIIa receptor antagonists are used upstream of PCI. Early myocardial infarction was reduced by an invasive strategy based on TACTICS-TIMI 18 data at 30 days; relative risk 0.53 (95% confidence interval 0.35 to 0.79). Intermediate myocardial infarction was not decreased by an invasive strategy although significant heterogeneity p<0.01 was detected when 6 month data from TACTICS-TIMI 18 were combined with 1 year data from ICTUS. The cause for this heterogeneity may be that, in contrast to ICTUS, the TACTICS-TIMI 18 investigators did not routinely measure CK-MB post-PCI (Table 2).

Death or Myocardial Infarction (Index, Early, Intermediate):

Data for this end point 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) relative risk of 0.67 (95% confidence interval 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 being 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; relative risk 0.50 (95% confidence interval 0.32 to 0.79). Troponin negative patients did not show significant benefit at 30 days follow up; relative risk 1.13 (95% confidence interval 0.49 to 2.63) although this confidence interval overlaps with those of troponin positive patients. In contrast, at intermediate (6 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 (6 months) benefits of an invasive strategy with relative risks of 0.47 (95% confidence interval 0.30 to 0.73) and 0.67 (95% confidence interval 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.

Analysis 3: Routine stent use but no routine glycoprotein IIb/IIIa receptor antagonist use. RITA-3, FRISC-II & VINO 2002

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 6-12 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 admission ECG. Mortality, assessed at 1 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 at 2 years and RITA-3 at 5 years and was significant improved by an invasive strategy (see analysis 1).

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; relative risk 2.22 (95% confidence interval 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 4 month RITA-3 data, was not significantly altered by an early invasive strategy. Intermediate (6 month data from VINO and 12 month data from FRISC-II and RITA-3) and late myocardial infarction (2 year FRISC-II data and 5 year RITA-3) data were significantly decreased by the invasive strategy; relative risk 0.72 (95% confidence interval 0.52 to 0.98) and relative risk 0.75 (95% confidence interval 0.61 to 0.91) 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; relative risk 2.07 (95% confidence interval 1.42 to 3.03). Possible reasons for the trend to hazard are similar to those discussed above for index myocardial infarction. 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 is possible that these patients have the most to gain from an invasive strategy. Late death or non-fatal myocardial infarction, based on the 2 year results from FRISC-II and 5 year results of RITA-3 is described in analysis 1.

The FRISC-II data showed that the benefit of the invasive strategy in the end-point of intermediate (6-12 month) death or non-fatal myocardial infarction was only significant in patients with ST depression at entry. The relative risk for this end point was 0.66 (95% confidence interval 0.50 to 0.88) at 6 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 relative risk of 0.71 (95% confidence interval 0.53 to 0.93) at 12 months whereas participants with TnT <0.1 ng/ml had only a trend for benefit with a relative risk of 0.77 (95% confidence interval 0.53 to 1.11). Again, the confidence intervals 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 (1 year) death or non-fatal myocardial infarction endpoint was only decreased significantly in the group of patients with both TnT >0.03 ng/ml and ST depression >0.1 mV; relative risk 0.60 (95% confidence interval 0.43 to 0.82).

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; relative risk 2.05 (95% confidence interval 1.56 to 2.70). 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 endpoint (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).

Bleeding

The invasive strategy was associated with an increased risk of bleeding; relative risk 1.71 (95% confidence interval 1.34 to 2.19). 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 ~8% of patients in the invasive arm compared to 5% of patients in the conservative arm.

Contrast Reactions:

Allergic reactions due to 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 depends on the proportion that undergoes subsequent angiography and this will depend 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 effects model altered the interpretation of the data. Most notably the early and intermediate myocardial infarction end point in analysis 1 showed a significant benefit as a result of the 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 estimates were the most consistent and robust findings of this meta-analysis and, in general, were not associated with significant heterogeneity. Further, the composite end point of death or non-fatal myocardial infarction was not reported by the ICTUS investigators and hence this end point was not subjected to sensitivity analysis. 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 3-5 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 6 hours of randomization. The excess events in the late invasive arm occurred prior to angiography; this was observed despite background antithrombotic 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 2 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 2.5-2.8% 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 analyzed separately as were data for TACTICS-TIMI 18 and VINO. When the high-mortality rate studies and low-mortality rate studies were analyzed separately, the previously reported findings of the review were not altered.

Percentage Of Trial Participants With a Positive Troponin:

Findings on subgroup analysis have 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 range between 50% and 75% (Table 1). The studies that only randomized biomarker-positive patients (VINO and ICTUS) were analyzed separately and showed a null effect on intermediate mortality. When the studies that did not specify cardiac biomarker status as an inclusion criterion were analyzed separately, there was a significant increase in index death in the invasive arm; relative risk 1.72 (95% confidence interval 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 multivessel disease (Rihal 2003) and reduce death over long term follow up (Yusuf 1994). 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 ~20% while RITA-3, FRISC-II and VINO had rates of ~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 & 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 (35 to 39%) compared to the other included trials (17 to 25%). When the former trials were pooled, a significant reduction in intermediate death was noted; relative risk 0.49 (95% confidence interval 0.25 to 0.95). This suggests as the difference in rates of revascularization between invasive and conservative arms narrows, the beneficial effect on mortality 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 relative risk of 1.59 (95% confidence interval 0.96 to 2.64). Early death (<4 months) and intermediate death (6-12 months) were not significantly improved with an invasive strategy and 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. Late death (2-5 years) was significantly decreased by an invasive strategy with a relative risk of 0.75 (95% confidence interval 0.62 to 0.92) based on data from two trials that provided long term follow up. Index myocardial infarction was not significantly improved with an early invasive strategy; significant heterogeneity was found on combining data. Myocardial infarction data at index hospitalization from trials that routinely used glycoprotein IIb/IIIa receptor antagonists were only available from TACTICS-TIMI 18 which showed a significant benefit of the early invasive strategy with a relative risk ratio of 0.61 (95% confidence interval 0.38 to 0.98). Early and intermediate myocardial infarction was not improved with an invasive strategy and significant heterogeneity was

found at these time points. Late myocardial infarction (2-5 years) was significantly improved by an invasive strategy with a relative risk of 0.75 (95% confidence interval 0.61 to 0.91) based on data from two trials that provided long term follow up. The ICTUS trial did not provide data for the composite end point of death or non-fatal myocardial infarction. Analysis of available data for this end point suggest that benefits of an early invasive strategy were significant only in trial participants with high risk characteristics i.e. positive troponin or ST depression on admission ECG. 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 confidence intervals 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 relative risk 0.47 (95% confidence interval 0.32 to 0.68) and intermediate relative risk 0.67 (95% confidence interval 0.55 to 0.83). Early and intermediate rehospitalization were both significantly decreased with an early invasive strategy; early relative risk 0.60 (95% confidence interval 0.41 to 0.88) and intermediate relative risk 0.67 (95% confidence interval 0.61 to 0.74). With regards to safety end points, the invasive strategy was associated with a two fold increase in the relative risk of the variably defined procedural myocardial infarction end point and a 1.7 fold increase in the relative risk of bleeding, but no increase in relative risk of stroke. The excess in bleeding is mainly due to wound site bleeding but is 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" i.e. 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 confidence interval 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 6 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 being seen in the ICTUS trial compared to other trials wherein, in both arms, early use of clopidogrel and intensive lipid-lowering therapy were recommended to treating clinicians. Disparate event rates in patients with positive troponin highlights the importance of global risk stratification as opposed to using cardiac bio-markers 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 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 6 months. Surprisingly, patients with angiographic CAD who had a negative troponin had a 5.8% rate of death or re-infarction at 6 months which is clearly higher than that for troponin positive patients without 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 and troponin positivity has also been shown to predict benefit from glycoprotein IIb/IIIa receptor antagonists (Hamm 1999; Heeschen 1999b) and remain 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 1 year (Cannon 1997). 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 disease was approximately 50% and 66% respectively in patients who had ST depression on admission ECG. 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/non-fatal myocardial infarction/rehospitalization for ACS. Using this end point, the relative risk was 0.62 (95% confidence interval 0.53 to 0.74) in participants with baseline ST changes while a null effect was observed in those without such changes. 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 sub-analysis 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% relative risk reduction. However, the number of women in the included studies was small and this decreased power to detect benefit from an invasive strategy as is highlighted by the wide confidence intervals. Women with UA/NSTEMI differ from men with the condition and this warrants further discussion.

The included studies have shown that women exhibit less severe coronary artery disease and are 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 relative risk 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 analyzed 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 but 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.

The importance of global risk stratification:

As the above discussion highlights and as sub-group 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 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 AHA guidelines recommend the use of several parameters for risk stratification (Braunwald 2002) e.g. 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 sub-analyses based on TIMI risk scores. The participants were stratified into 3 categories based on their TIMI risk score; low, intermediate or high risk. The study showed that only intermediate and high risk patients benefited from the invasive strategy with regards 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 compo-

nents 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 at six weeks and one year (Scirica 2002). Further, the TIMI risk score was also validated for the death, myocardial infarction or recurrent ischemia end point at up to 6 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 also 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 5 year follow up by the RITA-3 investigators, 9 factors other than treatment group emerged as multivariate 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.

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 6 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 1999-2002 were 5.9% for patients with NSTEMI and 2.7% for patients with unstable angina. Also, the 6 month post-discharge mortality rates were 6.2% and 3.6% for NSTEMI and unstable angina respectively (Goldberg 2005). Further, re-hospitalization rates at 6 months post-discharge were about 20%. In another report from the GRACE registry that included patients recruited between 1999 and 2003, the 6 month post-discharge mortality rates were reported as 11.6% from 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 ~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) and 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 which promoted optimal medical management and risk stratification. This implies that only progressively higher risk patients will continue to benefit from early invasive intervention in the future. Alternatively, lack of benefit in regards to several end points in this review may be due to lower-risk patients being selected for trial enrolment.

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

Two trials that were undertaken in the pre-stent era: TIMI-3b and VANQWISH 1998. The early invasive arm of TIMI-3b 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 endpoints 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 6 weeks and 1 year with relative risks of 0.54 (95% confidence interval 0.40 to 0.74) and 0.79 (95% confidence interval 0.68 to 0.93) respectively (TIMI-3b). In TIMI-3b, 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 with relative risks of 3.47 (95% confidence interval 1.41 to 8.52), 2.53 (95% confidence interval 1.19 to 5.42) and 1.60 (95% confidence interval 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 percent of patients in the invasive arm of this trial underwent a revascularization procedure; 47% of which involved CABG. The mortality associated with CABG in the invasive arm was 11.6% compared to 3.4% in the conservative arm and 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. Further, the VANQWISH protocol stipulated that beta-blocker and heparin use be physician initiated.

Not surprisingly, two recent meta-analyses on this topic that included the aforementioned old trials and the MATE 1998 trial reached different conclusions to the ones presented here (please see table of excluded studies for exclusion reasons). These reviews did not include the most recent trial, the ICTUS study. The review by Mehta et al showed that an invasive strategy was associated with mortality hazard from randomization to hospital discharge; relative risk 1.61 (95% confidence interval 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 analyzed 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 with relative risks of 0.78 (95% confidence interval 0.64 to 0.94) and 0.56 (95% confidence interval 0.47 to 0.68) respectively. This is consistent with the finding of late benefit in this review. When Mehta et al analyzed 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; relative risk 0.77 (95% confidence interval 0.67 to 0.89). The null effect on mortality observed may be driven by early hazard of an invasive strategy seen in older trials e.g. VANQWISH. This review analyzed the endpoints at certain time points since it was felt that combining outcomes collected from studies with short duration (6 months) with those of long duration (5 years) would not provide a meaningful point estimate (see table of included studies). Indeed, a significant risk reduction in mortality with an invasive strategy was only evident in trials with long term follow up. A significant reduction in recurrent angina and rehospitalization with an invasive strategy was a consistent finding across all reviews (Choudhry 2005; Mehta 2005).

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 6-12 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 25% relative risk reduction for both the end points of death and myocardial infarction assessed at 2-5 years, 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.

Implications for research

This review has highlighted the deficit in the data that exist to answer the important question of whether a routine early invasive strategy is superior to a conservative, ischemia-guided strategy in the optimal management of UA/NSTEMI in current practice. The trials have enrolled heterogeneous populations of patients with variable levels of risks and event rates, and subject to varying co-interventions, and have used outcome measures subject to variable definition and timing. Risk stratification of the participants in each trial based on a validated risk system (e.g. 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: all patients accounted for by end of trial; 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 & routine angiography (average 4d). 10% glycoprotein 2b/3a receptor antagonist use
Outcomes	death all causes (6, 12, 24 months), non-fatal MI (6, 12, 24 months), refractory angina (6 months), death or non-fatal MI (6, 12, 24 months), 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: six 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 & an elevated cardiac troponin T >0.3 microg/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 & routine angiography median time 23 hours post-randomization. 94% glycoprotein 2b/3a receptor antagonist use
Outcomes	death all causes (1 year), non-fatal MI (1 year), rehospitalization (1 year)
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

RITA-3 (*Continued*)

Participants	1810 patients with chest pain within the last 72 hours, a documented history of coronary artery disease (CAD) & 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, enoaxaparin invasive arm: as above & routine angiography (median 2d for angiogram). 25% glycoprotein 2b/3a receptor antagonist use
Outcomes	death all causes (4, 12, 24 months, 5 years), non-fatal 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; subanalyses reported on TIMI risk score & troponin status
Interventions	conservative arm: aspirin, beta blocker, UFH, tirofiban, statin invasive arm: as above & routine angiography (median 22h for angiogram). 94% glycoprotein 2b/3a receptor antagonist use
Outcomes	death all causes (30 days, 6 months), refractory angina (6 months), death or non-fatal MI (30 days, 6 months), rehospitalization (30 days, 6 months)
Notes	

VINO 2002

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
Interventions	conservative arm: aspirin, beta blocker, UFH, invasive arm: as above & routine angiography (average 6.2h for angiogram post-randomization). 0% glycoprotein 2b/3a receptor antagonist use

VINO 2002 (*Continued*)

Outcomes	death all causes (30 days, 6 months), non-fatal 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
GUSTO2b	This is 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 is 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	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

DATA AND ANALYSES

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Index Death	4	6618	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.96, 2.64]
1.1 Routine glycoprotein IIb/IIIa receptor antagonist use	1	2220	Risk Ratio (M-H, Random, 95% CI)	1.99 [0.85, 4.62]
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	2	4267	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.62, 0.92]
5 Index Myocardial Infarction	4	6618	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.44, 2.34]
5.1 Routine glycoprotein IIb/IIIa receptor antagonist use	1	2220	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.38, 0.98]
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)	0.81 [0.59, 1.12]
7.1 Routine glycoprotein IIb/IIIa receptor antagonist use	2	3420	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.48, 2.02]
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	2	4267	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.61, 0.91]
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]