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# Ticlopidine versus oral anticoagulation for coronary stenting (Review)

Cosmi B, Rubboli A, Castelvetri CC, Milandri M

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[Intervention Review]

# Ticlopidine versus oral anticoagulation for coronary stenting

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## ABSTRACT

### Background

A two to four week course of ticlopidine plus aspirin following coronary stenting is considered effective in preventing thrombotic occlusion of the stented vessel and safe in regards to bleeding and peripheral vascular complications. However, rare, although potentially life-threatening haematological complications have been reported with this drug regimen.

### Objectives

To evaluate the efficacy and safety of ticlopidine plus aspirin versus oral anticoagulants after coronary stenting

### Search methods

Electronic search of the Cochrane Library, Medline, Embase from 1991 to June 1999; references from trials and experts.

### Selection criteria

Randomised controlled trials comparing ticlopidine plus aspirin versus oral anticoagulants (either with or without aspirin) after elective or bail out coronary stenting.

### Data collection and analysis

Three reviewers assessed trial quality and compiled data on outcomes including: total mortality, non fatal myocardial infarction and revascularization occurring within the first 30 days after hospitalization, stent thrombosis on angiography, major and minor bleeding, neutropenia, thrombocytopenia, thrombotic thrombocytopenic purpura.

### Main results

Four trials (n = 2436 patients) were included. Ticlopidine plus aspirin compared to oral anticoagulants significantly reduced the risk of non-fatal acute myocardial infarction and revascularization at 30 days, combined negative events (mortality, myocardial infarction, revascularization at 30 days) (RR: 0.41; 95% CI: 0.25 to 0.69; NNT for 30 days: 22; 95% CI: 14 to 45), and major bleeding (RR in high quality studies: 0.24 ; 95% CI: 0.07 to 0.79). Ticlopidine plus aspirin compared to oral anticoagulants significantly increased the risk of eutropenia,thrombocytopenia and neutropenia (RR 5; 95% CI: 1.08 to 13.07; NNT for 30 days: 142; 95% CI: 76 to 1000). Ticlopidine plus aspirin versus oral anticoagulation did not affect all cause mortality. Ticlopidine plus aspirin significantly reduced the risk of stent thrombosis (angiography) which was seen only on studies with blinded outcome assessment (RR: 0.14; 95% CI: 0.03 to 0.60; NNT for 30 days: 33; 95% CI:16 to 166). Minor bleeding was reported only in one study and no studies recorded thrombotic thrombocytopenic purpura (TTP).

**Authors' conclusions**

Ticlopidine plus aspirin after coronary stenting is effective in reducing the risk of the revascularization, non fatal myocardial infarction and bleeding complications when compared with oral anticoagulants. No effect is observed on total mortality. However, the haematological side effects of ticlopidine are still a matter of concern, and strict monitoring of blood-cell counts is recommended. Physicians should also be aware of the possibility of rare although potentially life-threatening complications such as TTP

## PLAIN LANGUAGE SUMMARY

**Ticlopidine plus aspirin is better than oral anticoagulants alone for reducing the risk of revascularization, non-fatal myocardial infarction and bleeding following stenting of coronary arteries**

Stents are placed in arteries around the heart (coronary arteries) to keep formerly blocked arteries open. A blood clot (thrombus) may form in the coronary artery after stenting and cause acute myocardial infarction (fatal or non-fatal) or more surgery. Blood thinners must be given for a short time to prevent clotting. Ticlopidine plus aspirin reduce the risk of complications after coronary stenting with less bleeding when compared to standard treatment (oral anticoagulants). Ticlopidine plus aspirin have other side effects such as bone marrow toxicity. Strict monitoring of blood-cell counts is recommended during treatment.

## BACKGROUND

Coronary stenting has been proven highly effective in treating acute or subacute vessel closure after balloon angioplasty (Sigwart 1987) and in preventing restenosis in de novo lesions and vein grafts (Fischman 1994; Serruys 1994). Its clinical use was initially limited by two major drawbacks: the risk of stent thrombosis and the complications associated with an aggressive anticoagulation treatment. The inherent thrombogenicity of the metallic stent was in fact initially considered crucial in the development of stent thrombosis (and subsequent vessel closure), warranting aggressive antiplatelet/antithrombotic treatment with aspirin, dipyridamole, dextran, heparin and warfarin. This regimen, however, did not completely prevent stent thrombosis (and associated clinical sequelae such as myocardial infarction, need for emergency percutaneous or surgical revascularization or death) (Fischman 1994; Serruys 1994). Moreover this regimen was shown to be accompanied by bleeding and/or vascular complications which can seriously limit the benefits of coronary stenting.

More recently, anticoagulants were substituted by a pure antiplatelet treatment with ticlopidine for four weeks and aspirin indefinitely (Colombo 1995). This regimen, now representing the gold standard after coronary stenting, is considered to be effective in reducing both the thrombotic occlusion of the stented vessel (and the associated clinical events) and the hemorrhagic and peripheral vascular complications (Leon 1998). It is estimated that more than 1 million patients worldwide had a percutaneous coronary intervention in 1998 with 50-60% of the cases involving a coronary stent (Steinhubl 1999). It is estimated that the percentage of patients receiving stent implantation after angioplasty is now almost 80-90% (GISE 2000). Currently, nearly all patients undergoing coronary stenting receive 2 to 4 weeks of ticlopidine plus aspirin after the procedure (Steinhubl 1999).

Recently, several case-reports and case-series have suggested that ticlopidine plus aspirin treatment after coronary stenting could be associated with an increased incidence of a potentially fatal complication, that is thrombotic thrombocytopenic purpura (TTP) (Bennett 1998; Steinhubl 1999). Before these reports, TTP due to ticlopidine treatment was considered a very rare adverse event. Case-reports and case-series can alert clinicians to potentially severe adverse drug reactions, but they cannot firmly establish the causal relationship between ticlopidine plus aspirin and TTP. Randomised clinical trials cannot evaluate the incidence of rare adverse events because their sample size is too small and calculated on the basis of the expected frequency of the primary outcomes. A sample size of several thousand patients would be necessary to evaluate the incidence of rare adverse events. Post-marketing surveillance systems might partly address this issue.

The purpose of this review is to evaluate the evidence regarding the effectiveness and safety of the use of ticlopidine plus aspirin after coronary stenting.

## OBJECTIVES

To assess the effects of ticlopidine and aspirin vs. anticoagulants (either with or without aspirin ) in the prevention of unstable angina, acute myocardial infarction, mortality, necessity of re intervention or coronary bypass grafting within 30 days after elective or bail-out coronary stenting.

We wish to test the following a priori hypothesis:
a) main comparison: the association of ticlopidine and aspirin is as efficacious as anticoagulants in the prevention of unstable angina, acute myocardial infarction, mortality, necessity of re intervention or coronary bypass grafting within 30 days after elective or emergency coronary stenting.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Criteria for considering studies for this review:
a) randomised controlled trials (RCTs) that is those trials with a randomised generation of allocation sequences such as the use of random number tables or computer random number generator .
b) quasi-randomised controlled trials that is those trials with quasi randomised generation of allocation according to date of birth or case record number (Dickersin 1996).

Priority was given to double blind trials in which patients, care providers and outcome assessors were unaware of treatment allocation. Thus bias due to patient suggestion should be minimized (Waller 1989). If double blind studies were not available, priority was given to studies with blinded outcome assessment. For the principal analysis, a trial was regarded as double blind if the word " double blind" is used to describe the trial or if it was stated that outcome assessors, care providers and patients were blinded to treatment allocation (Jadad 1996). To evaluate the impact and possibly to estimate the incidence of TTP after ticlopidine plus aspirin after coronary stenting, we chose to consider the following;

1. any prospective or retrospective observational study evaluating adverse events due to ticlopidine plus aspirin treatment after coronary stenting;
2. the total number of case-reports and case series of TTP after ticlopidine plus aspirin for coronary stenting in the literature. In spite of their limitations, the total number of cases reported in the literature could give an approximate indication of the rarity of this complication;
3. reports to the post-marketing surveillance systems world wide (indicated through World Health Organization) suggesting an association between ticlopidine plus aspirin and TTP.

#### Types of participants

Patients undergoing coronary stenting electively or in a bail-out setting after coronary angioplasty for coronary artery disease (stable angina, unstable angina, silent ischemia).

#### Types of interventions

All types of ticlopidine plus aspirin or acetyl salicylic acid (ASA) regimens versus;
oral anticoagulants (warfarin, acenocoumarol, phenprocoumon) with or without ASA;
or versus standard heparin;
or versus low molecular weight heparins.

#### Types of outcome measures

The primary outcome was the following:
a)

Secondary outcomes were the following:
a)

***Primary outcomes***

Combined outcome comprising total mortality, non-fatal myocardial infarction and revascularization occurring within the first 30 days after hospitalization.

***Secondary outcomes***

1. onset of unstable angina or stent thrombosis shown on angiography;
2. major and minor bleeding;
3. neutropenia, thrombocytopenia or TTP.

## Search methods for identification of studies

The search strategy was that adopted by the Collaborative Review Group Search Strategy.

The following were searched:

- the Cochrane Controlled Trials Register (Cochrane Library issue n.2 1999)
- The National Library of Medicine MEDLINE database systematically searched from January 1991 to December including a Cochrane Randomised Controlled Trials Filter for identification of randomised controlled trials as the following:

No. Records Request
1 73812 RANDOMIZED-CONTROLLED-TRIAL in PT
2 17750 CONTROLLED-CLINICAL-TRIAL in PT
3 8631 RANDOMIZED-CONTROLLED-TRIALS
4 11058 RANDOM-ALLOCATION
5 28941 DOUBLE-BLIND-METHOD
6 4086 SINGLE-BLIND-METHOD
7 112700 #1 or #2 or #3 or #4 or #5 or #6
8 968250 TG=ANIMAL
9 2311030 TG=HUMAN
10 968250 TG=ANIMAL
11 708155 (TG=ANIMAL) not ((TG=HUMAN) and (TG=ANIMAL))
12 105576 #7 not #11
13 141140 CLINICAL-TRIAL in PT
14 29096 explode CLINICAL-TRIALS/ all subheadings
15 712814 clin*
16 100359 trial*
17 6403 (clin* near trial*) in TI
18 712814 clin*
19 100359 trial*
20 27172 (clin* near trial*) in AB
21 199717 singl*
22 84596 doubl*
23 88 trebl*
24 12806 tripl*
25 50039 blind*
26 10872 mask*
27 36957 (singl* or doubl* or trebl* or tripl*) near (blind* or mask*)
28 26517 (#27 in TI) or (#27 in AB)
29 4587 PLACEBOS
30 31339 placebo*
31 4146 placebo* in TI
32 31339 placebo*
33 29821 placebo* in AB
34 119624 random*
35 14197 random* in TI
36 119624 random*
37 105428 random* in AB
38 8799 RESEARCH-DESIGN
39 240852 #13 or #14 or #17 or #20 or #28 or #29 or #31 or #33 or #35 or #37 or #38
40 968250 TG=ANIMAL
41 2311030 TG=HUMAN
42 968250 TG=ANIMAL
43 708155 (TG=ANIMAL) not ((TG=HUMAN) and (TG=ANIMAL))
44 223381 #39 not #43
45 120751 #44 not #12
46 370596 TG=COMPARATIVE-STUDY
47 122457 explode EVALUATION-STUDIES/ all subheadings
48 102973 FOLLOW-UP-STUDIES
49 72368 PROSPECTIVE-STUDIES
50 601464 control*
51 93622 prospectiv*
52 30711 volunteer*
53 686558 control* or prospectiv* or volunteer*
54 509652 (#53 in TI) or (#53 in AB)
55 950021 #46 or #47 or #48 or #49 or #54
56 968250 TG=ANIMAL
57 2311030 TG=HUMAN
58 968250 TG=ANIMAL
59 708155 (TG=ANIMAL) not ((TG=HUMAN) and (TG=ANIMAL))
60 727055 #55 not #59
61 576361 #60 not (#12 or #45)
62 802688 #12 or #45 or #61
63 802688 #62
64 893 ticlopid*
65 9593 stent*
66 4643 stent* in ti
67 9593 stent*
68 6730 stent* in ab
69 9593 stent*
70 7443 stent* in mesh
71 9489 #66 or #68 or #70
72 206 #64 and #71
73 69579 coronar*
74 25829 coronar* in ti
75 69579 coronar*
76 49325 coronar* in ab
77 69579 coronar*
78 51580 coronar* in mesh
79 14214 angioplas*
80 5164 angioplas* in ti
81 14214 angioplas*
82 9437 angioplas* in ab
83 14214 angioplas*
84 11280 angioplas* in mesh
85 73584 #74 or #76 or #78 or #80 or #82 or #84
86 196 #72 and #85
* 87 130 #86 and #63

MEDLINE: years Jan. 1991 - Dec 1999

For Adverse Drug Reaction

o. Records Request
1 216 exact{TICLOPIDINE-ADVERSE-EFFECTS} in *F

2 968250 TG=ANIMAL
3 2311030 TG=HUMAN
4 968250 TG=ANIMAL
5 708155 ((TG=ANIMAL) not (TG=HUMAN)) and (TG=ANIMAL)
6 216 #1 not #5
7 9593 stent*
8 4643 stent* in ti
9 9593 stent*
10 6730 stent* in ab
11 9593 stent*
12 7443 stent* in mesh
13 9489 #8 or #10 or #12
14 34 #6 and #13
15 69579 coronar*
16 25829 coronar* in ti
17 69579 coronar*
18 49325 coronar* in ab
19 69579 coronar*
20 51580 coronar* in mesh
21 14214 angioplas*
22 5164 angioplas* in ti
23 14214 angioplas*
24 9437 angioplas* in ab
25 14214 angioplas*
26 11280 angioplas* in mesh
27 73584 #16 or #18 or #20 or #22 or #24 or #26
* 28 34 #14 and #27

3. EMBASE searched from 1991-1998 using the following terms:
001 ticlopidine/ae
002 stent/
003 1 and 2
004 ticlopidine/ae and stent.mp. [mp=title, abstract, heading wo rd, trade name, manufacturer name]
005 (angioplas$ or coronar$).mp. [mp=title, abstract, heading word,
trade name, manufacturer name]
006 3 and 5

EMBASE: Jan. 1991 - March 1999

Adverse Drug Reaction

001 ticlopidine/ae 87
002 stent/ 1258
003 1 and 2 3
004 ticlopidine/ae and stent.mp. [mp=title, abstract, heading wo 3 rd, trade name, manufacturer name]
005 (angioplas$ or coronar$).mp. [mp=title, abstract, heading wo 16525
rd, trade name, manufacturer name]
006 3 and 5

Date of most recent searches: Dec 1999

In addition the following were reviewed:

1. Reference list of papers resulting from this search.
2. Recent conference proceedings of European and North American Societies for cardiovascular disease.
3. Pharmaceutical companies producing ticlopidine and investigators of primary studies were contacted to inquire if they are aware of any unpublished trials.

The database printouts of all citations identified were examined independently by three reviewers (CC, a non-expert of the content area with epidemiological background, and, MM a non-expert of the content area with clinical and epidemiological background; AR an expert of the content area) to identify potentially relevant primary studies, reviews and meta-analysis. The fourth reviewer cross checked and solved any discrepancies in selection (BC). All papers that either reviewer thought potentially relevant were obtained. The complete text was checked for additional potentially eligible reports of trials, and frequently cited papers were identified in order to enter them into SCISEARCH to retrieve additional reports which had cited these papers. Published and unpublished studies were considered, without language restriction (Egger 1997A).

## Data collection and analysis

### Selection of articles.

Two reviewers (CC, MM) selected potentially eligible articles for inclusion in the review. A study was considered potentially eligible if it was a prospective trial with at least two concurrent comparison groups, in which patients undergoing coronary stenting were allocated to a regimen with anticoagulant drugs (as defined above) or ticlopidine plus aspirin. Exclusion criteria were the following: studies with retrospective design, prospective non randomised studies. In order to assure clinical relevance of article selection, an expert of the content area (AR) independently determined eligibility as well. Any discrepancies were solved by a fourth reviewer (BC).

### Assessment of internal validity of trials

Internal validity reflects the degree to which the results of the trial are free of random error (due to chance) and systematic error (bias) (Fletcher 1988).
The methodological quality of each trial was assessed independently by each reviewer using the following scales as suggested by the Cochrane Collaborative Review Group.
1) A validated scale developed by (Jadad 1996) (which includes appropriateness of randomization and double blinding, a description of drop-outs and withdrawals). The Jadad scale includes three items with a maximum score of five points (two point each for randomization and double blinding, one point for withdrawals and drop-outs), however, it assesses neither concealment of allocation nor proportion and handling of drop-outs and withdrawals. Three or more points are required for a trial to be judged as high quality (Jadad 1996).

2) Items identified by Schulz et al (Schulz 1995) (allocation concealment and double-blinding). Quality score was assessed according to the criteria suggested by the Cochrane Collaboration Handbook (Mulrow 1997). Each trial was given an allocation score of A (clearly concealed), B (unclear if concealed) or C (clearly not concealed) and a summary score of A (low risk of bias), B (moderate risk of bias) or C (high risk of bias). Trials scoring A were included and those scoring C were excluded in sensitivity analysis. For trials scoring B, an attempt was made to obtain more information by contacting the author. If no or insufficient information was provided on a given component, no credit was given until further information can be obtained from primary authors. Assessment was done independently by three reviewers (CC, MM, AR). with the fourth reviewer (BC) independently cross-checking and solving disagreement.

### Data collection

The following data were abstracted on a standardized data collection form from each trial independently by three reviewers (CC, MM, AR), with the fourth reviewer (BC) independently cross-checking and solving discrepancies.

1. Publication type and sources, including language of publication, whether the report was peer-reviewed , year of publication, way of retrieval.
2. Sources of support.
3. Trial design , including the generation and concealment of allocation sequences and type of control intervention.
4. Setting , including country and level of care.
5. Inclusion/exclusion criteria of patients.
6. Diagnostic criteria for unstable angina.
7. Diagnostic criteria for stable angina.
8. Diagnostic criteria for silent ischemia.
9. Patient details (age, gender, co-morbidity).
10. Intervention including dose, route of administration, duration of treatment, compliance.
11. Outcomes measures : modalities and schedules of assessment; whether adverse events and overall mortality were recorded.
12. Analysis, including whether analysis was done according to the intention to treat principle, and type of statistical test used.
13. Results, including averages and variations of individual outcome assessments and different comparisons, test statistics and p-values for comparisons within and between groups.

Primary authors were contacted by means of questionnaires and, if necessary, telephone interviews, in order to obtain additional information.

### Statistical analyses

Our measure of effect for each study was the relative risk (RR). Approximate chi-square tests for heterogeneity were used to assess outcome data for compatibility with the assumption of a uniform relative risk (p >0.10). A random effects model was used to combine outcomes across studies. The weighting factor for each study is the inverse of the within study variance plus a between study variance component. Thus all pooled estimates are DerSimonian-Laird type random effect estimators. Pooled risk differences obtained from Der Simonian Laird (DerSimonian 1986) random effect model are converted to numbers needed to treat with the formula NNT=1/risk difference. NNT are the number of patients who must be treated to prevent one adverse outcome. The 95% confidence interval for NNT were computed as a simple inverse of the upper and lower values of the 95% confidence interval for risk difference.

To test for robustness of results, several sensitivity analyses were performed.
This included:
(i) analysing by both fixed effect and random effect models (DerSimonian 1986);
(ii) including only high quality trials as defined for the two quality assessment scales by Schulz et al. (Schulz 1995) and Jadad et al. (Jadad 1996); trials with a Jadad score equal or greater than 3 were analysed separately from trials with a Jadad score lower than 3;
(iii) including only RCTs with clearly adequate random generation of allocation sequences, adequate concealment of treatment allocation schedule, and adequate double-blinding and adequate follow-up, assessed as described above; trials without an adequate allocation concealment were analysed separately ;
(iv) exclusion of unpublished trials, and trials published only in abstract form;
(vi) we used a random effects regression model to examine sources of heterogeneity with respect of major bleeding. Different intensities of oral anticoagulation may account for the heterogeneity of bleeding outcomes among studies.

All of the analyses were based on the intention-to-treat data from the individual clinical trials. Treatment effects were defined as the proportion of patients experiencing the main and secondary outcomes in the ticlopidine and aspirin group when compared with the proportion of patients experiencing the same outcomes in the anticoagulation group. Analyses were also conducted in defined sub-group of patients : a) those undergoing elective stenting and b) those undergoing bail-out stenting. To examine the effect of binary outcomes, such as mortality, odds ratios were computed using a random effects model. Funnel plots were examined (Light 1984), possible asymmetry of the plots assessed adopting a regression approach by Egger et al (Egger 1997). Although of limited power, a chi-square-test was used to assess heterogeneity of trials (Hedges 1985) with the significance level set at p = 0.1.

We choose the internal validity score as an independent variable because there is evidence that lower internal validity is associated with an overestimation of treatment effects (Schulz 1995). Sample size is considered because of its relation to publication bias (Berlin 1989) and other reasons for asymmetrical funnel plots (Gotzsche 1992; Egger 1997).
Furthermore, the contribution of each trial to the overall statistics for heterogeneity was computed (Thompson 1993). Trials contributing most were further examined for possible sources of heterogeneity. Pre discussion agreement between reviewers regarding identification of potentially eligible trials, and definitive article selection was determined using the kappa coefficient (Cohen 1960). Pre discussion agreement regarding internal validity assessments was determined using the intra class correlation coefficient (Shrout 1979). Values above 0.60 were regarded as substantial (Landis 1977).

## RESULTS

### Description of studies

Eight randomised controlled trials were identified as eligible. The kappa coefficients regarding identification of potentially eligible trials and definite article selection were 0.42 and 0.28, respectively.

Four studies were excluded from the analysis for the following reasons; one study compared ticlopidine plus ASA plus enoxaparin versus anticoagulation (ENTICES); one study was a double report of the Entices trial (Zidar 1998); one study was excluded because it reported a sub-group analysis of a previous trial (Schulen 1997); one study was excluded because it considered the 6-month follow-up of a previous trial with the end-point of vessel restenosis (ISAR II).

The four remaining studies evaluated a total of 2436 patients (ISAR:517; FANTASTIC: 473; MATTIS 350; STARS: 1096).
All trials were multi centre in design. One trial was conducted in Germany (ISAR), two trials (FANTASTIC; MATTIS) were conducted

in several European countries (Belgium, Germany, Italy, the Netherlands, Sweden, UK and Turkey) and one trial (STARS) was conducted in the USA. None of the trials specified ethnicity. The study population was enrolled in tertiary care centres in all studies .The characteristics of each study are indicated in the Characteristics of Included Studies Table.

The diagnostic criteria for each outcome of interest was defined in all trials. The definitions were homogeneous for all outcomes except for bleeding complications and schedule and assessment criteria of hematological side-effects. The different criteria for the latter outcomes are indicated in the Characteristics of Included Studies Table.

## Risk of bias in included studies

None of the trials employed double blinding, however blinded outcome assessment of all end-points was employed in two studies (MATTIS; STARS) , while in one study (ISAR) only angiographic analyses and surveillance of the access site for bleeding were evaluated by blinded outcome assessors. Thus all trials were scored B on a Schulz scale, while on a Jadad score three studies scored 3 and 1 scored 2 (STARS). An attempt to contact the primary author of the latter study was unsuccessful. The kappa coefficient for methodological quality of the studies was 0.90. See 'Method' heading in the characteristics of included studies for a description of each study's method of randomisation and stratification if any.

## Effects of interventions

Analyses were performed on the combined results of all four studies and separately for the three studies with a Jadad score of 3 (FANTASTIC; ISAR; MATTIS) and for the studies with blinded outcome assessment (ISAR; MATTIS; STARS). We observed homogeneity across studies with respect to all outcomes except for stent thrombosis on angiography and major bleeding. No difference in relative risk was observed when calculated according to a fixed or a random effect model except for stent thrombosis on angiography, major bleeding and bleeding from the vascular access site. The funnel plots showed that studies of different size seemed equally scattered around the pooled estimate. The existence of a relevant publication/retrieval bias, however, cannot be excluded due to the low number of trials evaluated.

### Total mortality

None of the individual studies showed a benefit of ticlopidine plus aspirin. The combined results of all studies indicated a lack of benefit of ticlopidine plus aspirin (RR: 0.73, 95% CI: 0.25 to 2.18).

### Non-fatal acute myocardial infarction

Of the individual studies only the STARS trial reported a significant effect of ticlopidine plus aspirin (STARS). The combined results of the four trials indicated a benefit of ticlopidine plus aspirin (RR: 0.50 95% CI:0.3 to 0.83; 30 days NNT = 55; 95% CI:34 to 142). When only studies with a Jadad score > 3 (FANTASTIC; ISAR; MATTIS) were considered, the RR was 0.56 (95%CI 0.31 to 0.98; 30 days NNT = 38; 95% CI: 22 to 142). When only the studies with blinded outcome assessment (MATTIS; STARS) were considered , the RR was 0.40 (95% CI:0.18 to 0.85; 30 days NNT = 50; 95% CI:33 to 333) in favour of ticlopidine plus aspirin.

### Revascularization within 30 days

Of the individual studies only ISAR and STARS reported a significant effect of ticlopidine plus aspirin (ISAR; STARS).
The combined results of the three trials (ISAR; MATTIS; STARS) reporting data on this end-point indicated a benefit of ticlopidine plus aspirin (RR: 0.29 95% CI: 0.16 to 0.56; 30 days NNT = 33; 95% CI:20 to 100). When only studies with a Jadad score > 3 (ISAR; MATTIS) were considered, the RR was 0.33 (95%CI 0.16 to 0.69; 30 days NNT = 23; 95% CI:14 to 55). When only studies with blinded outcome assessment (MATTIS; STARS) were considered, the RR was 0.33 (95% CI: 0.16 to 0.70; 30 days NNT = 38; 95% CI:20 to 1000) in favour of ticlopidine plus aspirin.

### Total primary outcome

Of the individual studies, STARS, MATTIS and ISAR reported a significant effect of ticlopidine plus aspirin (STARS; MATTIS; ISAR).
The combined results of the four trials indicated a benefit of ticlopidine plus aspirin (RR: 0.41 95% CI:0.25 to 0.69; 30 days NNT = 22; 95% CI: 14 to 45). When only studies with a Jadad score > 3 (FANTASTIC; ISAR; MATTIS) were considered, the RR was 0.48 (95%CI 0.28 to 0.82; 30 days NNT = 18; 95% CI:11 to 44). When only studies with blinded outcome assessment (MATTIS; STARS) were considered, the RR was 0.38 (95% CI:0.18 to 0.81; 30 days NNT = 22; 95% CI:10 to 500) in favour of ticlopidine plus aspirin.

### Stent thrombosis on angiography

Of the individual studies only ISAR and STARS reported a significant effect of ticlopidine plus aspirin (ISAR; STARS). The FANTASTIC trial reported a significant effect of ticlopidine plus aspirin only on subacute (>24 hours) stent occlusion (FANTASTIC). The combined results of the three trials reporting data on this end-point did not indicate a benefit of ticlopidine plus aspirin (RR: 0.26 95% CI:0.06 to 1.14) when calculated with a random effect model and a significant heterogeneity between studies was observed. The intensity of anticoagulation (high INR range-3.5 -4.5- in ISAR; low INR range -2.0-3.0- in FANTASTIC and STARS) did not explain the heterogeneity (ISAR, FANTASTIC, STARS). However, when only studies with blinded outcome assessment were considered (ISAR and STARS) no heterogeneity was observed and the RR was 0.14 (95% CI: 0.03 to 0.60; 30 days NNT = 29; 95% CI:16 to 166) in favour of ticlopidine plus aspirin.

### Major bleeding

Of the four individual studies ISAR, FANTASTIC, MATTIS reported a significant effect of ticlopidine plus aspirin in reducing the risk of bleeding (ISAR, FANTASTIC, MATTIS). The combined results of the four trials indicated a RR of 0.36 (95% CI: 0.14 to 1.02) with a significant heterogeneity between studies (p = 0.01). This was due to the STARS trial in which the rate of bleeding events was the same in ticlopidine plus aspirin and anticoagulation groups (STARS). When only studies with blinded outcome assessment were considered (MATTIS; STARS) the RR was 0.53 (95% CI: 0.15 to 1.05; 30 days NNT = 37; 95% CI: 14 to 55), with significant heterogeneity between studies. When only studies with a Jadad score > 3 were considered and thus the STARS trial was excluded from the analysis, the RR was 0.24 (95% CI 0.07 to 0.79; 30 days NNT = 18; 95% CI:13 to 30) in favour of ticlopidine plus aspirin with no significant heterogeneity between studies. The intensity of anticoagulation (high INR range-3.5-4.5- ISAR and low INR range

-2.0-3.0- in FANTASTIC and STARS) did not explain the heterogeneity among studies (ISAR; FANTASTIC; STARS).

When bleeding at the vascular access site was considered, ISAR reported a significant effect of ticlopidine plus aspirin in reducing the risk of complications and FANTASTIC reported a significant reduction in the rate of ecchymosis > 5 cm due to the treatment (ISAR; FANTASTIC). When all studies were analysed for this outcome, the RR was 0.41 (95% CI: 0.19 to 0.88; 30 days NNT = 16; 95% CI:8 to 250) in favour of ticlopidine plus aspirin with a significant heterogeneity between studies (p = 0.03). This heterogeneity might be due to the different intensity of peri-procedural anticoagulation, which however was difficult to quantify because of the different regimens adopted in the studies. In particular, the STARS trial reported an equal number of complications in the anticoagulation and ticlopidine plus aspirin group (STARS). When studies with a Jadad score > 3 were analyzed with the exclusion of the STARS trial, the RR was 0.37 (95% CI:0.09 to 0.77; 30 days NNT = 12; 95% CI:6 to 55) with significant heterogeneity among studies (STARS). When studies with blinded outcome assessment (ISAR,MATTIS,STARS) were considered, the RR was 0.30 (95% CI:0.07 to 1.36) in favour of ticlopidine plus aspirin with significant heterogeneity among studies. When studies with a Jadad score > 3 and a blinded outcome assessment were considered (ISAR; MATTIS) the RR was 0.14 (95% CI:0.05 to 0.41; 30 days NNT = 18; 95% CI:13 to 32) in favour of ticlopidine plus aspirin with no heterogeneity among studies.

#### Minor bleeding

Only FANTASTIC study reported data on this end-point and no significant difference was reported between ticlopidine plus aspirin and anticoagulation groups (RR: 0.75 to 95% CI:0.46 to 1.21) (FANTASTIC).

#### Neutropenia/leukopenia/thrombocytopenia

None of the individual studies reported a significant effect of ticlopidine plus aspirin in increasing the risk of these haematological side-effects. However, the combined results of the four trials indicated a significant effect of ticlopidine plus aspirin (RR : 5 ;95% CI:1.08 to 23.07; 30 days NNT = 142; 95% CI:76 to 1000) compared to anticoagulation. When only studies with blinded outcome assessment were analyzed, the RR was 4.09 (95% CI: 0.68 to 24.60; 30 days NNT = 142; 95% CI:52 to 166).
No cases of thrombotic thrombocytopenic purpura were reported in any of the trials.

#### Subgroup analyses

None of the studies indicated the rate of outcomes in subgroup of patients such as those undergoing either elective or bailout stenting or receiving different types of stenting in the same study. However, the efficacy of treatment was not influenced by the type of stents used in the different trials.
The exception was the FANTASTIC trial in which ticlopidine plus aspirin was more effective than oral anticoagulation in elective stenting (RR:0.24; 95% CI: 0.07 to 0.85) but not in unplanned stenting (RR: 1.10; 95% CI: 0.44 to 2.77) in reducing the risk of total cardiac related events of death and re-infarction (FANTASTIC).

## DISCUSSION

### Methods

Randomised clinical trials evaluating the efficacy of ticlopidine plus aspirin after coronary stenting versus oral anticoagulation or alternative treatment were all conducted in an open label fashion. The lack of double blinding may introduce bias when evaluating the study outcomes, however two studies performed blinded assessment on all efficacy and safety outcomes (MATTIS, STARS) while one study conducted blinded outcome assessment regarding angiographic data and vascular access site bleeding (ISAR).

### Efficacy

Studies included patients with different degrees of disease severity, different stenting procedures and also different peri-procedural treatment. No benefit was observed on the outcome of total mortality, while a significant benefit was observed on non-fatal acute myocardial infarction and revascularization at 30 days. When the total composite outcome of total mortality, non fatal acute myocardial infarction and revascularization at 30 days was considered, a significant benefit of ticlopidine plus aspirin was observed when compared to oral anticoagulants in all the analyses performed. ISAR and STARS included only patients with successful stent implantation whereas FANTASTIC and MATTIS have also included "bail out" procedures i.e. higher risk patients. These two studies are closer to the common practice which may explain the different rates of major cardiac events (ISAR; STARS; FANTASTIC; MATTIS).

When stent thrombosis on angiography was considered no significant effect of ticlopidine plus aspirin was observed, except when only studies with blinded outcome assessment were considered. In this case no heterogeneity among studies was observed and the RR was 0.14 (95% CI:0.03 to 0.60) in favour of ticlopidine plus aspirin. Only one study evaluated acute stent thrombosis (< 24 hour) separately from subacute stent thrombosis (> 24 hours). The intensity of oral anticoagulation did not seem to influence the rate of stent thrombosis.

### Safety

When adverse events were considered, a significant increase in the risk of major bleeding was observed in the group treated with anticoagulants only in high quality studies. These data should be interpreted with caution because the criteria for classification of the severity of bleeding were heterogeneous between studies. The intensity of oral anticoagulant treatment was different among studies, with three studies employing a low INR range and one study employing a high INR range. The intensity of anticoagulation did not influence the risk of bleeding.

A significant effect of ticlopidine plus aspirin in reducing the risk of complications at the vascular access site was observed in high quality studies.
Minor bleeding was reported only in one study and a non significant difference was observed between ticlopidine plus aspirin and anticoagulation. When haematological side effects were considered, the events were rare, however ticlopidine plus aspirin increased significantly the risk of these complications when compared to anticoagulation. The assessment criteria and schedule for haematological side-effects were not consistently

defined in all studies. As a result some cases may have been missed especially after hospital discharge.

### Subgroup analyses

Data could not be analyzed separately for subgroups of patients, as planned, such as patients receiving different types of stents or those undergoing elective versus bailout stenting. The exception was the FANTASTIC trial in which a subgroup analysis indicated that ticlopidine plus aspirin was significantly effective in reducing the risk of the total primary outcome in patients undergoing elective stenting when compared to oral anticoagulation and no effect was reported on those patients undergoing unplanned stenting (FANTASTIC). Caution must be exercised in the interpretation of these data due to the lack of blinded outcome assessment in this trial.

### Rare adverse events

Randomised clinical trials are not designed to evaluate rare adverse events. When thrombotic thrombocytopenic purpura (TTP) was considered, none of the four trials reported cases of TTP.

We retrieved 35 additional RCTs, prospective or retrospective observational studies (Albiero 1997; Antonellis 1999; Antoniucci 1997; Bage 1998; Barragan 1994; Berger 1998; Berger 1999; Carrillo Anaya 1996; Clarkson 1999; Colombo 1995; Goods 1996; Goods 1996b; Goods 1996c; Hall 1996; Heublein 1998; Iturbe 1997; Karillon 1996; Lablanche 1996; Madan 1998; Markert 1996; Martinez Elbal 1998; Morice 1995; Moussa 1999; Nakamura 1997; Park 1997a; Park 1999; Serruys 1996; Spadaro 1999; Steinhubl 1999; Valdes 1996; Van Belle 1995; Wilson 1999; Zemour 1995; Zubaid 1995; ENTICES), evaluating ticlopidine plus aspirin for coronary stenting in a total of 55235 patients. Among these studies, only one (Steinhubl 1999) reported 9 cases of TTP after the retrospective evaluation of 43322 patients who were treated with ticlopidine plus aspirin after coronary stenting in the USA. The incidence of TTP resulted to be 0.02% (95% CI: 0.04% to 0.009%). The schedule and criteria for assessment of haematological side-effects were widely heterogeneous among these studies. Case reports or case-series were found for a total of 79 cases of TTP (Bennett 1998; Bennett 1998b; Chen 1999; Jamar 1998). The Uppsala WHO Monitoring centre did not report any cases of TTP related to ticlopidine plus aspirin after coronary stenting.

## AUTHORS' CONCLUSIONS

### Implications for practice

The benefits of ticlopidine plus aspirin when compared with oral anticoagulants after coronary stenting are significant on the composite outcome of total mortality, revascularization and non fatal myocardial reinfarction, due to the effect on the reduction of the two latter outcomes. The association of ticlopidine plus aspirin has replaced oral anticoagulants and it is now the standard treatment after coronary stenting in many countries. The haemorrhagic events are significantly reduced by ticlopidine plus aspirin when compared to oral anticoagulants. The haematological side effects of ticlopidine are still a matter of concern, and strict monitoring of blood-cell counts is recommended .

### Implications for research

Ticlopidine is an effective antithrombotic drug, however, the risk of potentially serious adverse events has prompted the development of potentially safer alternatives. This field is rapidly evolving and most likely additional studies using ticlopidine and its analogues will be reported in the future. This may include studies with clopidogrel, a thienopirydine analogue of ticlopidine which has been tested in a large phase III RCTs trial in the prevention of cardiovascular events in high risk patients (CAPRIE 1996). It has also been evaluated in RCTs in association with aspirin after coronary stenting. Although the RCTs indicated a lower incidence of haematological toxicity of clopidogrel when compared to ticlopidine, recently, a case series of 11 patients with TTP after clopidogrel has been published (Bennett 2000). Our preliminary data also indicate that a greater effort should be made to monitor the drug related adverse events in the post-marketing surveillance systems.

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* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

**FANTASTIC**

| | |
|---|---|
| Methods | Multicenter study<br>Randomization method:stated<br>Randomization before stenting for unplanned stenting and before angioplasty for elective procedures;<br>No double blinding<br>No blinded outcome assessment<br>Stratification: no<br>Losses to follow-up and drop-outs: 12/485<br>Intention-to-treat analysis: no<br>Compliance evaluated: no |
| Participants | All patients with planned and unplanned coronary stenting<br>Characteristics of patients at baseline: similar<br>Age: mean 60 .<br>Men: 80%<br>Previous AMI: |

**FANTASTIC** *(Continued)*

| | |
|---|---|
| | 49%,<br>previous CABG:14%<br>previous PTCA:33.5%<br>unstable angina: 42%<br>stable angina: 49.5%<br>Comorbidity:<br>Diabetes mellitus: 15%<br>Hypertension: 32%<br>Current smokers: 30%<br>Dyslipidemia: 45%<br>Exclusion criteria: known bleeding disorders, thrombocytopenia < 150.000/mm3,<br>recent (<6 months) gastrointestinal bleeding, recent cerebrovascular accident, recent intracranial or eye surgery, severe hepatc or renal dysfunction, malignant hypertension, angiographic evidence of thrombus at the proposed stent site, history of allergy to ASA or ticlopidine, history of hepain related thrombocytopenia, reduced life expectancy |
| Interventions | Pre-procedural:<br>ASA 100-300 mg/day<br>Peri-procedural:<br>heparin bolus of 10,000 U followed by 5000 U boluses for each additional hour of procedure. No further heparin was given to patients who left the cath lab before 2 PM and their femoral artery sheaths were removed 4 hours later. In the remaining patients, the sheaths were removed the following day. These patients received an intravenous infusion of heparin 1000 U/h until 6 AM the next day . The sheaths were removed 4 hours after discontinuation of heparin.<br>Type of stent: Wiktor<br>inflation pressure: >10 atm<br>elective stent in 50% (236/473) Post-procedural<br>Anticoagulation group : ASA 100-325 mg od for life + heparin bolus 2500 U after sheath removal followed by 1000 U / hour heparin infusion adjusted to achieve an activated partial thromboplastin time 2.0-2.5 times control + oral anticoagulants immediately after stent implantation adjusted to target INR 2.5-3.0. When target INR documented for 2 consecutive days , heparin infusion was discontinued.<br>ASA+ oral anticoagulants<br>for 6 weeks<br>Antiplatelet therapy group: ticlopidine first (500 mg) in cath lab followed by ticlopidine 250 mg bid +ASA 100 -325 mg bid for 6 weeks. If ticlopidine was stopped within 4 weeks after stent implantation it was recommended that it be replaced by oral<br>anticoagulation<br>continued until 6 weeks after stent implantation. If ticlopidine was stopped after 4 weeks after stent implantation , it was recommended that it be replaced by dipyridamole (450 mg) daily until six weeks after stent implantation. |
| Outcomes | Total mortality non fatal myocardial infarction, stent<br>thrombosis on angiography, bleeding complications<br>were subdivided depending on whether they were local complications (at the vascular access site), further subdivided into ecchymoses, haematomas or false aneurysms or occurred at another site - intracranial,gastrointestinal,intraocular, macroscopic hematuria,any bleeding that required blood transfusion, minor bleeding, leukopenia,<br>skin rashes, duration of hospitalization<br>Schedule and assessment criteria for hematological side-effects: blood cell counts performed at 2 weeks, 1 month and 6 weeks after stent implantation.<br>If the white cell count was between 1200 and 1700/mm3 or the platelet count was between 80,000 and 150,000 /mm3 it was recommended to obtain a blood count every 2 days and to continue the treatment. If the white cell count fell to < 1200/mm3 and/or the pletelet count to < 80,000/mm3, it was recommended to stop treatment and a blood count was to be obtained 1 and 2 weeks later or more frequently of judged necessary. |
| Notes | |

***Risk of bias***

**FANTASTIC** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | A - Adequate |

**ISAR**

| | |
|---|---|
| Methods | Multicenter study<br>Randomization method: stated<br>Randomization after successful stenting<br>No double blinding<br>Blinded outcome assessment of angiographic analyses and vascular access site ( severe peripheral vascular events)<br>Stratification: no<br>Losses to follow-up : no<br>Intention-to-treat: yes<br>Compliance evaluated: no |
| Participants | All patients after successful stenting of coronary artery or venous bypass graft (e.g: all pt. in whom stent was placed in the desired position and with < 30% residual stenosis).<br>Characteristics of patients at baseline: similar<br>Age: mean 61.<br>Men: 76%<br>Previous AMI:43%<br>Acute AMI: 23%<br>Unstable angina:<br>44%<br>previous CABG: 10%<br>previous PTCA: 19%<br>Comorbidity:<br>Diabetes mellitus: 17%<br>Hypertension: 63%<br>Current smokers: 53%<br>Dyslipidemia: 34%<br><br>Exclusion criteria:<br>contraindication to the use of ASA, ticlopidine or anticoagulation, pt. with cardiogenic shock and in those patients who had needed mechanical ventilation before undergoing PTCA and in patients in whom stenting was intended primarily as a bridge to CABG |
| Interventions | Pre-procedural: not stated<br>Peri-procedural:<br>heparin 15.000 U + ASA 500 mg intravenously.<br>When the activated partial thromboplastin time fell below 60 secs, the arterial sheath was removed (tipically 3 hours after the procedure), manual compression of the groin -at least 30 min. -followed by application of pressure bandage.<br>After application of pressure bandage,<br>heparin infusion titrated to obtain an activated partial thromboplastin time of 80-100 seconds was started in all patients.<br>Type of stent: Palmaz-Schatz<br>inflation pressure: 15.8-16 atm<br><br>Post-procedural:<br>Anticoagulation group: ASA 100 mg bid + heparin infusion continued for 5-10 days until stable degree of oral anticoagulation was achieved + phenprocoumon with target INR 3.5-4.5<br>for 4 weeks<br>Antiplatelet therapy group: |

**ISAR** *(Continued)*

| | |
|---|---|
| | heparin infusion discontinued 12 hours after stent placement, ticlopidine 250 mg bid +ASA 100 mg bid for 4 weeks |
| Outcomes | Total mortality, non fatal myocardial infarction, revascularization within 30 days - PTCA or CABG, stent thrombosis on angiography,<br>bleeding complications:<br>events requiring surgery or transfusion (indicated if haemoglobin fell below 8 gr/dL) bleeding associated with objective signs of organ dysfunction;<br>peripheral severe vascular events were pseudo aneurysms or arteriovenous fistulas at access site requiring surgery or prolonged ultrasound guided compression.<br>Schedule and assessment criteria for haematological side-effects:<br>blood counts not performed after hospital discharge |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | A - Adequate |

**MATTIS**

| | |
|---|---|
| Methods | Multicenter study<br>Randomization method: stated<br>Randomization after successful stenting<br>Stratification:<br>according to stent categories (n.4)<br>No double blinding<br>Blinded outcome assessment of all outcomes<br>Losses to follow-up : no<br>Intention-to-treat: yes<br>compliance evaluated: yes |
| Participants | High risk patients after implantation procedure e.g. 1 or more of the following conditions: bail-out stenting, suboptimal results with residual stenosis > 20%,<br>multiple stent implantations, nominal diameter of largest ballon inflated<2.5mm<br>Characteristics of patients at baseline: similar<br>Age: mean 60<br>Men: 80%<br>previous AMI: 49.1%;<br>previos CABG: 9%;<br>previous PTCA: 23%;<br>Comorbidity:<br>Diabetes mellitus: 15%<br>Hypertension: 37%<br>Current smokers: 20%<br>Dyslipidemia: 47%<br>Indication for stenting:<br>post-AMI: 19%<br>unstable angina: 39%<br>stable angina: 37%<br>silent ischemia: 5%<br>Exclusion criteria: |

**MATTIS** *(Continued)*

| | |
|---|---|
| | recent AMI, persistent ischemia, age < 18 , pregnancy, administration of GP IIb/IIIa antagonists, ongoing OAC treatment, coronary reintervention planned within 30 days of follow-up, previous participation in any study within 30 days |
| Interventions | Pre- procedural: not stated<br>Peri-procedural:<br>heparin dose not specified. In pt assigned to antiplatelet regimen duration of heparin infusion was a maximum of 36 hours and discontinued 6 hours before sheath removal.<br>type of stent: Palmaz-Schatz (19%), Wiktor (4.5%), Gianturco-Robin (4.5%), other stents (72%, Microstents, NIR, Multilink, Pura, Wallstent); inflation pressure: not specified<br>bail-out stenting: in 32.5% (114/350) of patients<br><br>Post-procedural<br>Anticoagulation group: ASA 250 mg od + heparin+ warfarin started on day of randomization with target INR 2.5-3.0 for 30 days. Heparin infusion was discontinued when INR was documented > 2.5 for two consecutive days.<br>Antiplatelet therapy group: ticlopidine 250 mg bid ( first daily dose 500 mg given on one intake in the first day of randomization+<br>ASA 250 mg od for 30 days |
| Outcomes | Total mortality (cardiovascular)<br>non fatal myocardial infarction, revascularization within 30 days,<br>stent thrombosis on angiography, bleeding complications were one or more of the following: vascular access site requiring surgical repair, any bleeding leading to a decrease of haemoglobin > 4 gr/dL and/or requiring transfusion of > 2 U of blood, documented intracranial or retroperitoneal bleeding, leukopenia<br>hepatitis, sk,in reactions .<br>Schedule and assessment criteria for haematological side-effects:<br>blood cell counts on day 15, 30 and 5 and 6 weeks after the procedure.<br>No criteria given to evaluate degree of cytopenia.No rules given for treatment interruption in case of cytopenia. |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | A - Adequate |

**STARS**

| | |
|---|---|
| Methods | Multicenter study<br>Randomization method: unclear<br>Stratification: according to clinical site and diabetes mellitus<br>No double blinding<br>Blinded outcome assessment of all outcomes<br>Loss to follow-up: no but not specified<br>Intention-to-treat: yes<br>compliance evaluated:<br>no |
| Participants | Patients after successful stenting of 1-2 target lesions > 60% stenosis in 3-4<br>mm native coronary artery<br>not involving left coronary artery or a major coronary bifurcation<br>Characteristics of patients at baseline: similar |

**STARS** *(Continued)*

| | |
|---|---|
| | Age: mean 61,<br>Men: 70%<br>Previous AMI: 35%<br>previous PTCA: 16%<br>previous CABG: 7.5%<br>angina of grade III or IV: 60%<br>Comorbidity:<br>Diabetes mellitus: 19%<br>Hypertension: 52%<br>Current smokers: 29%<br>Dyslipidemia: 33%<br>Exclusion criteria:<br>additional stenoses in the target vessel, recent AMI in the previous 7 days, contraindication to ASA, ticlopidine or warfarin, history of bleeding diathesis, current treatment with abciximab, planned angioplasty of another lesion within 30 days after enrolment. |
| Interventions | Pre-procedural: not specified<br>Peri-procedural:<br>generic non-enteric coated ASA 325 mg +<br>heparin infusion 10,000-15,000 titrated to maintain an activated clotting time of 250-300 seconds. No further heparin was given after the procedure except among patients assigned to receive warfarin.<br>Type of stent:<br>Palmaz-Schatz<br>inflation pressure: >16 atm<br>Post-procedural<br>Anticoagulation group: ASA 325 mg od + warfarin with INR 2.0-2.5 for 4 weeks. First dose of warfarin at conclusion of stenting procedure + heparin<br>with the dose titrated to achieve an activated partial thromboplastin time of 40-60 seconds. Heparin infusion lasted for several days (5-10 days) and discontinued until an INR of 2.0.2.5 was obtained.<br><br>Antiplatelet therapy group 1:<br>non enteric coated ASA 325 mg daily for 4 weeks.<br>Antiplatelet therapy group 2:<br>ticlopidine 250 mg bid +ASA 325 mg od for 4 weeks<br>First dose of ticlopidine at conclusion of stenting procedure. |
| Outcomes | Total mortality<br>non fatal myocardial infarction, revascularization within 30 days, stent thrombosis on angiography, cerebrovascular accidents, vascular site surgical complications,<br>bleeding, leukopenia<br>Criteria for bleeding:<br>a major bleeding complication was defined as any procedure-related bleeding episode that required transfusion.<br>Vascular surgical complications included any retroperitoneal haematoma, vascular access haematoma of more than 4 cm, pseudoaneurysm or arteriovenous fistula requiring surgery of ultrasonographic compression.<br>Schedule and assessment criteria for haematological side-effects:<br>two complete blood counts were perfomed two and four weeks after the stenting procedure , with neutropenia defined as absolute white-cell count less than 1200 per cubic millimeter and thrombocytopenia as a reduction in the platelet count to below 80,000 per cubic millimeter.<br>No criteria given for treatment interruption in case of cytopenia. |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | B - Unclear |

AMI: acute myocardial infarction
PTCA: percutaneous coronary angioplasty
CABG: coronary artery bypass graft
INR: International Normalized Ratio
ASA: acetil salicylic acid (aspirin)
GP IIb/IIIa antagonists: platelet glycoprotein GPIIb/IIIa antagonists
OAC: oral anticoagulants

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

| Study | Reason for exclusion |
|---|---|
| ENTICES | type of intervention not included in our methods (e.g ticlopidine plus aspirin plus low molecular weight heparin was compared to oral anticoagulation) |
| ISAR II | 6 month- follow up of included trial ( ISAR) with end-point of vessel restenosis |
| Schulen 1997 | sub-group analysis of included trial ( ISAR) was reported |
| Zidar 1998 | double report of ENTICES |

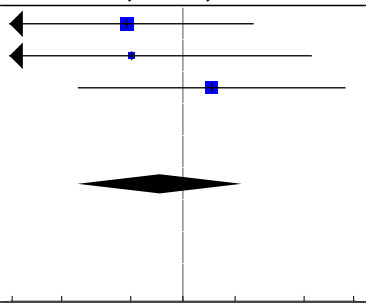
## DATA AND ANALYSES

### Comparison 1. total mortality

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 total mortality | 4 | 2436 | Risk Ratio (M-H, Random, 95% CI) | 0.73 [0.25, 2.18] |

### Analysis 1.1. Comparison 1 total mortality, Outcome 1 total mortality.

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| FANTASTIC | 2/243 | 4/230 | | 41.68% | 0.47[0.09,2.56] |
| ISAR | 1/257 | 2/260 | | 20.71% | 0.51[0.05,5.54] |
| MATTIS | 3/177 | 2/173 | | 37.61% | 1.47[0.25,8.67] |
| STARS | 0/546 | 0/550 | | | Not estimable |
| **Total (95% CI)** | **1223** | **1213** | | **100%** | **0.73[0.25,2.18]** |
| Total events: 6 (Treatment), 8 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.94, df=2(P=0.63); $I^2$=0% | | | | | |
| Test for overall effect: Z=0.56(P=0.58) | | | | | |

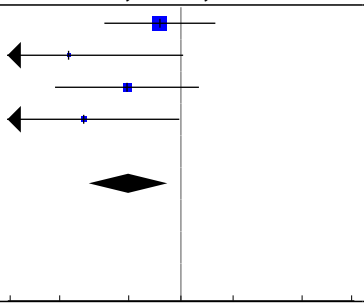


## Comparison 2. non fatal myocardial infarction

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 non fatal myocardial infarction | 4 | 2436 | Risk Ratio (M-H, Random, 95% CI) | 0.50 [0.29, 0.83] |
| 2 non-fatal AMI in Jadad score 3 studies | 3 | 1340 | Risk Ratio (M-H, Random, 95% CI) | 0.56 [0.31, 0.98] |
| 3 non fatal AMI in Jadad score <3 studies | 1 | 1096 | Risk Ratio (M-H, Random, 95% CI) | 0.27 [0.08, 0.98] |

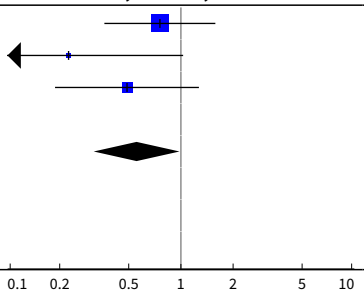
### Analysis 2.1. Comparison 2 non fatal myocardial infarction, Outcome 1 non fatal myocardial infarction.

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| FANTASTIC | 12/243 | 15/230 | | 44.69% | 0.76[0.36,1.58] |
| ISAR | 2/257 | 9/260 | | 11.41% | 0.22[0.05,1.03] |
| MATTIS | 6/177 | 12/173 | | 27.71% | 0.49[0.19,1.27] |
| STARS | 3/546 | 11/550 | | 16.18% | 0.27[0.08,0.98] |
| **Total (95% CI)** | **1223** | **1213** | | **100%** | **0.5[0.29,0.83]** |
| Total events: 23 (Treatment), 47 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0.02; $Chi^2$=3.17, df=3(P=0.37); $I^2$=5.48% | | | | | |
| Test for overall effect: Z=2.64(P=0.01) | | | | | |




### Analysis 2.2. Comparison 2 non fatal myocardial infarction, Outcome 2 non-fatal AMI in Jadad score 3 studies.

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| FANTASTIC | 12/243 | 15/230 | | 53.31% | 0.76[0.36,1.58] |
| ISAR | 2/257 | 9/260 | | 13.62% | 0.22[0.05,1.03] |
| MATTIS | 6/177 | 12/173 | | 33.07% | 0.49[0.19,1.27] |
| **Total (95% CI)** | **677** | **663** | | **100%** | **0.56[0.31,0.98]** |
| Total events: 20 (Treatment), 36 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0.02; $Chi^2$=2.13, df=2(P=0.35); $I^2$=5.98% | | | | | |
| Test for overall effect: Z=2.02(P=0.04) | | | | | |



### Analysis 2.3. Comparison 2 non fatal myocardial infarction, Outcome 3 non fatal AMI in Jadad score <3 studies.

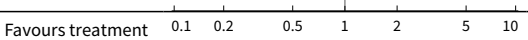
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| STARS | 3/546 | 11/550 | | 100% | 0.27[0.08,0.98] |
| **Total (95% CI)** | **546** | **550** | | **100%** | **0.27[0.08,0.98]** |
| Total events: 3 (Treatment), 11 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.99(P=0.05) | | | | | |


## Comparison 3. revascularization within 30 days

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 revascularization within 30 days | 3 | 1963 | Risk Ratio (M-H, Random, 95% CI) | 0.29 [0.16, 0.56] |
| 2 revascularization within 30 days Jadad score 3 | 2 | 867 | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.16, 0.69] |
| 3 revascularization within 30 days Jadad score<3 | 1 | 1096 | Risk Ratio (M-H, Random, 95% CI) | 0.22 [0.06, 0.75] |

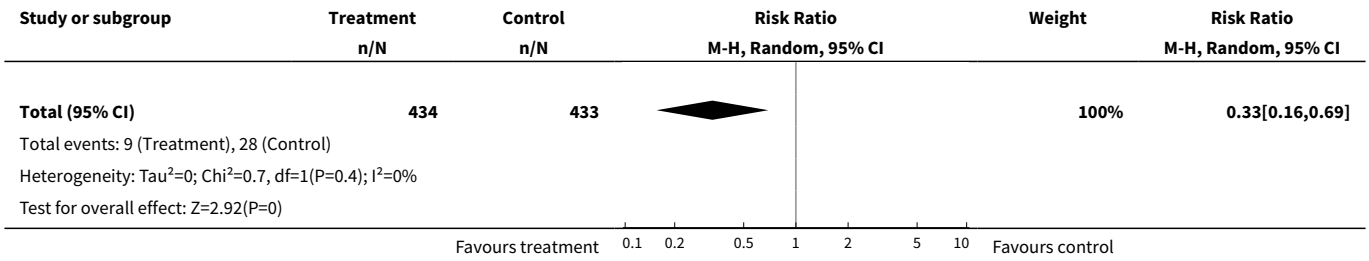
### Analysis 3.1. Comparison 3 revascularization within 30 days, Outcome 1 revascularization within 30 days.

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| ISAR | 3/257 | 14/260 | | 26.73% | 0.22[0.06,0.75] |
| MATTIS | 6/177 | 14/173 | | 46.82% | 0.42[0.16,1.06] |
| STARS | 3/546 | 14/550 | | 26.46% | 0.22[0.06,0.75] |
| **Total (95% CI)** | **980** | **983** | | **100%** | **0.29[0.16,0.56]** |
| Total events: 12 (Treatment), 42 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.04, df=2(P=0.6); $I^2$=0% | | | | | |
| Test for overall effect: Z=3.75(P=0) | | | | | |

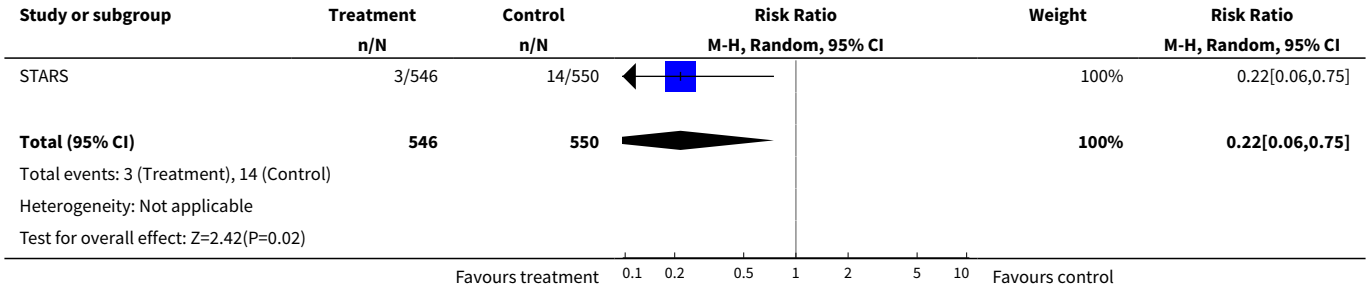



### Analysis 3.2. Comparison 3 revascularization within 30 days, Outcome 2 revascularization within 30 days Jadad score 3.

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| ISAR | 3/257 | 14/260 | | 36.34% | 0.22[0.06,0.75] |
| MATTIS | 6/177 | 14/173 | | 63.66% | 0.42[0.16,1.06] |



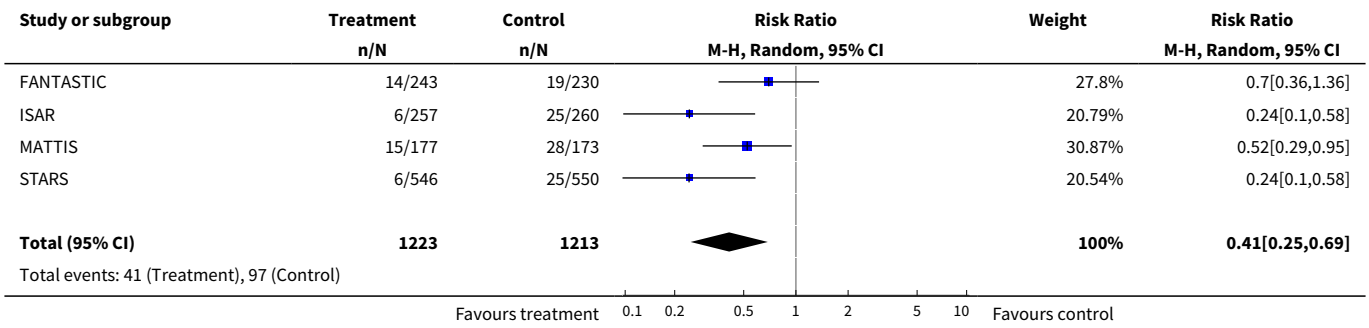

### Analysis 3.3. Comparison 3 revascularization within 30 days, Outcome 3 revascularization within 30 days Jadad score<3.

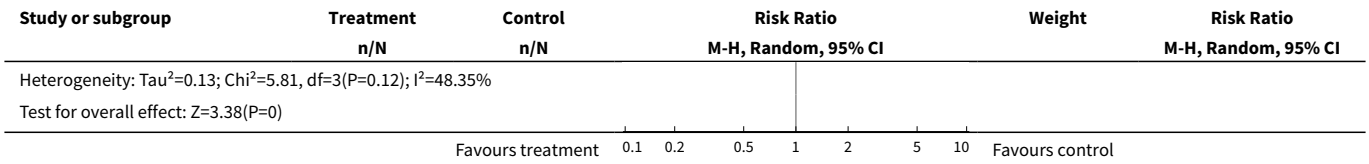



## Comparison 4. total primary outcome

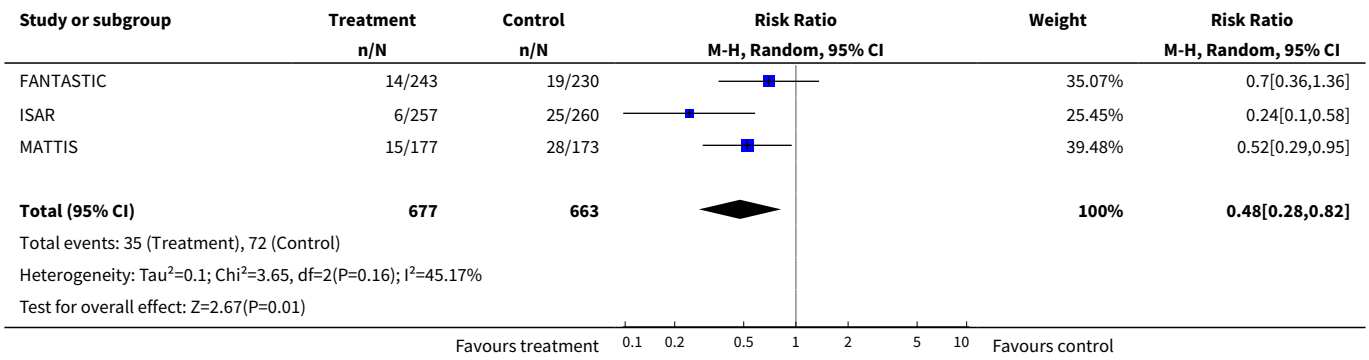
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 total primary outcome | 4 | 2436 | Risk Ratio (M-H, Random, 95% CI) | 0.41 [0.25, 0.69] |
| 2 total primary outcome Jadad score 3 | 3 | 1340 | Risk Ratio (M-H, Random, 95% CI) | 0.48 [0.28, 0.82] |
| 3 total primary outcome Jadad score<3 | 1 | 1096 | Risk Ratio (M-H, Random, 95% CI) | 0.24 [0.10, 0.58] |

### Analysis 4.1. Comparison 4 total primary outcome, Outcome 1 total primary outcome.

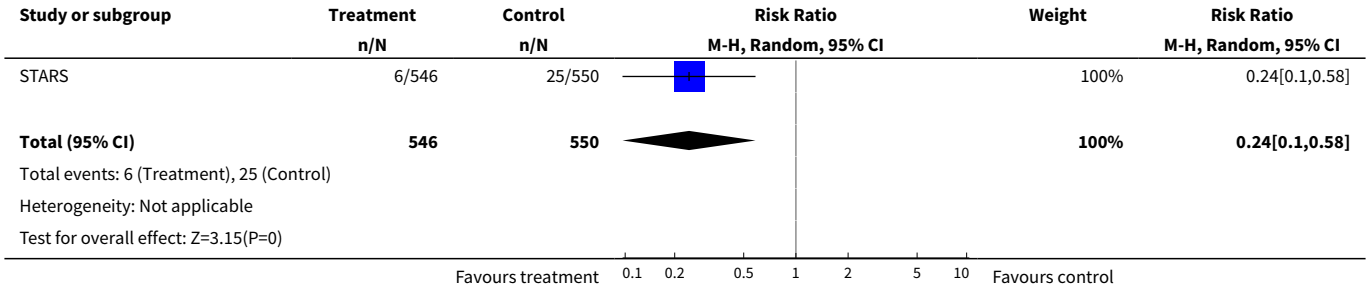





### Analysis 4.2. Comparison 4 total primary outcome, Outcome 2 total primary outcome Jadad score 3.




### Analysis 4.3. Comparison 4 total primary outcome, Outcome 3 total primary outcome Jadad score<3.




## Comparison 5. stent thrombosis on angiography

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 stent thrombosis on angiography | 3 | 2086 | Risk Ratio (M-H, Random, 95% CI) | 0.26 [0.06, 1.14] |
| 2 stent thrombosis on angiography Jadad score 3 | 2 | 990 | Risk Ratio (M-H, Random, 95% CI) | 0.21 [0.01, 5.67] |
| 3 stent thrombosis on angiography Jadad score<3 | 1 | 1096 | Risk Ratio (M-H, Random, 95% CI) | 0.20 [0.06, 0.69] |
| 4 stent thrombosis on angiography Fantastic+Stars | 2 | 1569 | Risk Ratio (M-H, Random, 95% CI) | 0.41 [0.11, 1.47] |

### Analysis 5.1. Comparison 5 stent thrombosis on angiography, Outcome 1 stent thrombosis on angiography.

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| FANTASTIC | 7/243 | 9/230 | | 43.1% | 0.74[0.28,1.94] |
| ISAR | 0/257 | 13/260 | | 18.19% | 0.04[0,0.63] |
| STARS | 3/546 | 15/550 | | 38.71% | 0.2[0.06,0.69] |
| **Total (95% CI)** | **1046** | **1040** | | **100%** | **0.26[0.06,1.14]** |
| Total events: 10 (Treatment), 37 (Control) | | | | | |
| Heterogeneity: $Tau^2$=1.08; $Chi^2$=6.13, df=2(P=0.05); $I^2$=67.35% | | | | | |
| Test for overall effect: Z=1.78(P=0.07) | | | | | |




### Analysis 5.2. Comparison 5 stent thrombosis on angiography, Outcome 2 stent thrombosis on angiography Jadad score 3.

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| FANTASTIC | 7/243 | 9/230 | | 57.85% | 0.74[0.28,1.94] |
| ISAR | 0/257 | 13/260 | | 42.15% | 0.04[0,0.63] |
| **Total (95% CI)** | **500** | **490** | | **100%** | **0.21[0.01,5.67]** |
| Total events: 7 (Treatment), 22 (Control) | | | | | |
| Heterogeneity: $Tau^2$=4.64; $Chi^2$=5.02, df=1(P=0.03); $I^2$=80.07% | | | | | |
| Test for overall effect: Z=0.93(P=0.35) | | | | | |




### Analysis 5.3. Comparison 5 stent thrombosis on angiography, Outcome 3 stent thrombosis on angiography Jadad score<3.

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| STARS | 3/546 | 15/550 | | 100% | 0.2[0.06,0.69] |
| **Total (95% CI)** | **546** | **550** | | **100%** | **0.2[0.06,0.69]** |
| Total events: 3 (Treatment), 15 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=2.54(P=0.01) | | | | | |

### Analysis 5.4. Comparison 5 stent thrombosis on angiography, Outcome 4 stent thrombosis on angiography Fantastic+Stars.

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| FANTASTIC | 7/243 | 9/230 | | 54.38% | 0.74[0.28,1.94] |
| STARS | 3/546 | 15/550 | | 45.62% | 0.2[0.06,0.69] |
| **Total (95% CI)** | **789** | **780** | | **100%** | **0.41[0.11,1.47]** |
| Total events: 10 (Treatment), 24 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0.54; $Chi^2$=2.68, df=1(P=0.1); $I^2$=62.71% | | | | | |
| Test for overall effect: Z=1.37(P=0.17) | | | | | |




## Comparison 6. major bleeding

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 major bleeding | 4 | 2436 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.14, 1.02] |
| 2 major bleeding Jadad score 3 | 3 | 1340 | Risk Ratio (M-H, Random, 95% CI) | 0.24 [0.07, 0.79] |
| 3 major bleeding Jadad score <3 | 1 | 1096 | Risk Ratio (M-H, Random, 95% CI) | 0.89 [0.55, 1.43] |

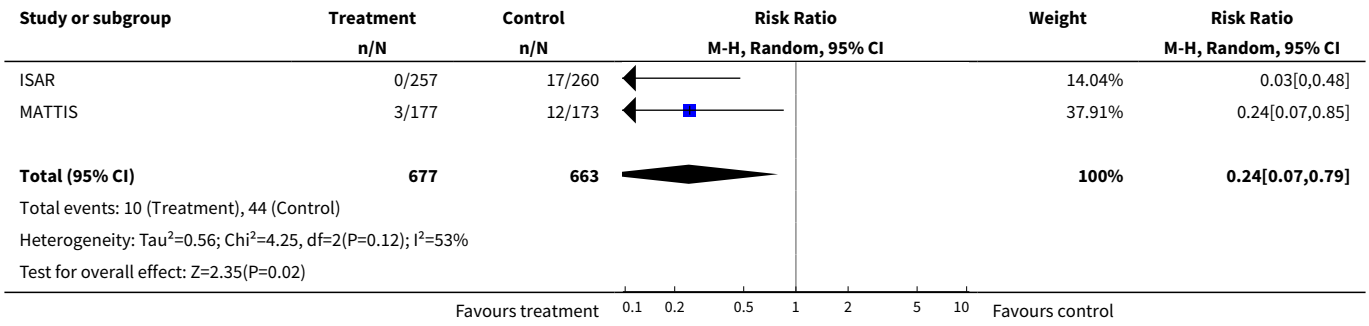
### Analysis 6.1. Comparison 6 major bleeding, Outcome 1 major bleeding.

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| FANTASTIC | 7/243 | 15/230 | | 30.13% | 0.44[0.18,1.06] |
| ISAR | 0/257 | 17/260 | | 9.36% | 0.03[0,0.48] |
| MATTIS | 3/177 | 12/173 | | 24.2% | 0.24[0.07,0.85] |
| STARS | 30/546 | 34/550 | | 36.32% | 0.89[0.55,1.43] |
| **Total (95% CI)** | **1223** | **1213** | | **100%** | **0.38[0.14,1.02]** |
| Total events: 40 (Treatment), 78 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0.63; $Chi^2$=10.63, df=3(P=0.01); $I^2$=71.78% | | | | | |
| Test for overall effect: Z=1.92(P=0.05) | | | | | |

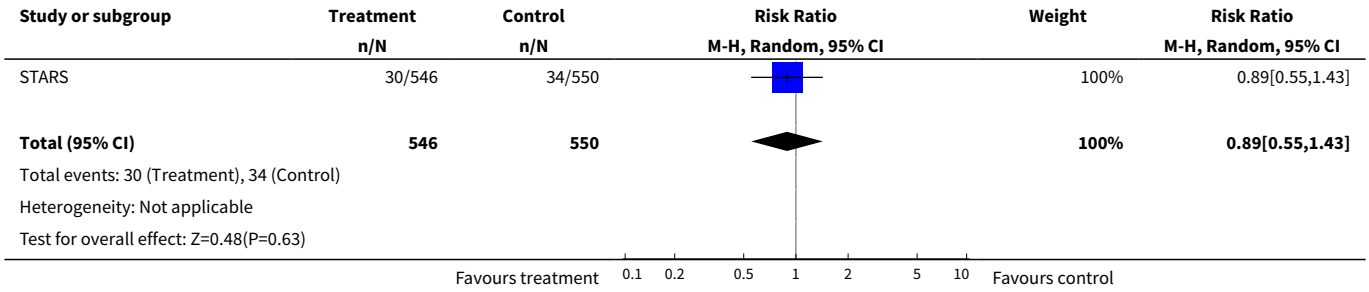



### Analysis 6.2. Comparison 6 major bleeding, Outcome 2 major bleeding Jadad score 3.

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| FANTASTIC | 7/243 | 15/230 | | 48.05% | 0.44[0.18,1.06] |



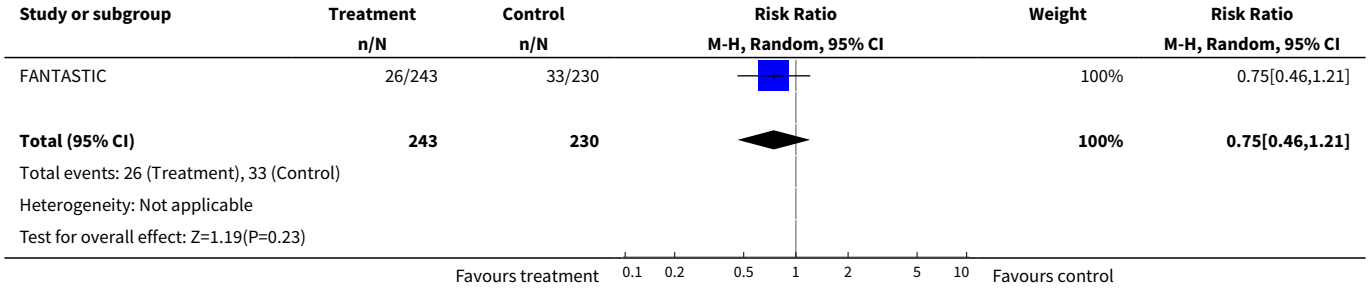

### Analysis 6.3. Comparison 6 major bleeding, Outcome 3 major bleeding Jadad score <3.




## Comparison 7. minor bleeding

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 minor bleeding | 1 | 473 | Risk Ratio (M-H, Random, 95% CI) | 0.75 [0.46, 1.21] |

### Analysis 7.1. Comparison 7 minor bleeding, Outcome 1 minor bleeding.

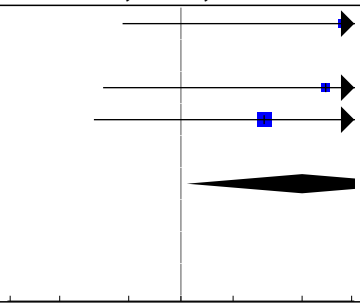


## Comparison 8. neutropenia/leukopenia/thrombocytopenia

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 neutropenia/leukopenia/thrombocytopenia | 4 | 2436 | Risk Ratio (M-H, Random, 95% CI) | 5.00 [1.08, 23.07] |
| 2 Jadad score 3 | 3 | 1340 | Risk Ratio (M-H, Random, 95% CI) | 7.65 [0.96, 60.96] |
| 3 Jadad score <3 | 1 | 1096 | Risk Ratio (M-H, Random, 95% CI) | 3.02 [0.32, 28.96] |

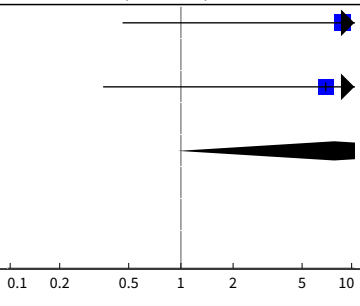
### Analysis 8.1. Comparison 8 neutropenia/leukopenia/thrombocytopenia, Outcome 1 neutropenia/leukopenia/thrombocytopenia.

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| FANTASTIC | 4/243 | 0/230 | | 27.49% | 8.52[0.46,157.38] |
| ISAR | 0/257 | 0/260 | | | Not estimable |
| MATTIS | 3/177 | 0/173 | | 26.75% | 6.84[0.36,131.5] |
| STARS | 3/546 | 1/550 | | 45.76% | 3.02[0.32,28.96] |
| **Total (95% CI)** | **1223** | **1213** | | **100%** | **5[1.08,23.07]** |
| Total events: 10 (Treatment), 1 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.37, df=2(P=0.83); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.06(P=0.04) | | | | | |



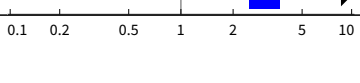

### Analysis 8.2. Comparison 8 neutropenia/leukopenia/thrombocytopenia, Outcome 2 Jadad score 3.

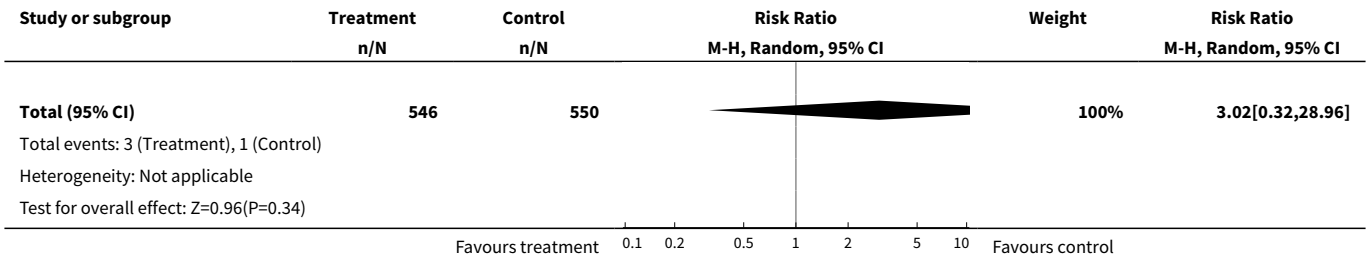
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| FANTASTIC | 4/243 | 0/230 | | 50.67% | 8.52[0.46,157.38] |
| ISAR | 0/257 | 0/260 | | | Not estimable |
| MATTIS | 3/177 | 0/173 | | 49.33% | 6.84[0.36,131.5] |
| **Total (95% CI)** | **677** | **663** | | **100%** | **7.65[0.96,60.96]** |
| Total events: 7 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.01, df=1(P=0.92); $I^2$=0% | | | | | |
| Test for overall effect: Z=1.92(P=0.05) | | | | | |




### Analysis 8.3. Comparison 8 neutropenia/leukopenia/thrombocytopenia, Outcome 3 Jadad score <3.

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| STARS | 3/546 | 1/550 | | 100% | 3.02[0.32,28.96] |

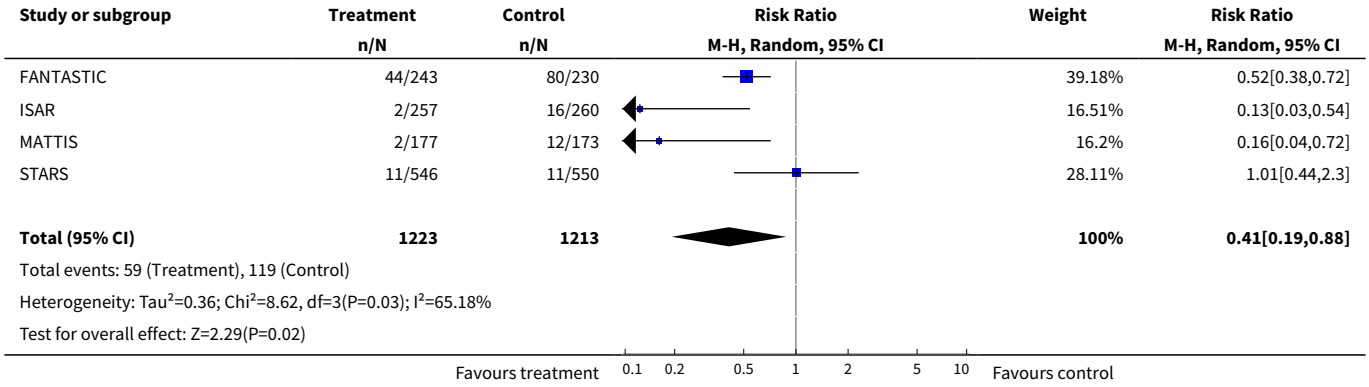




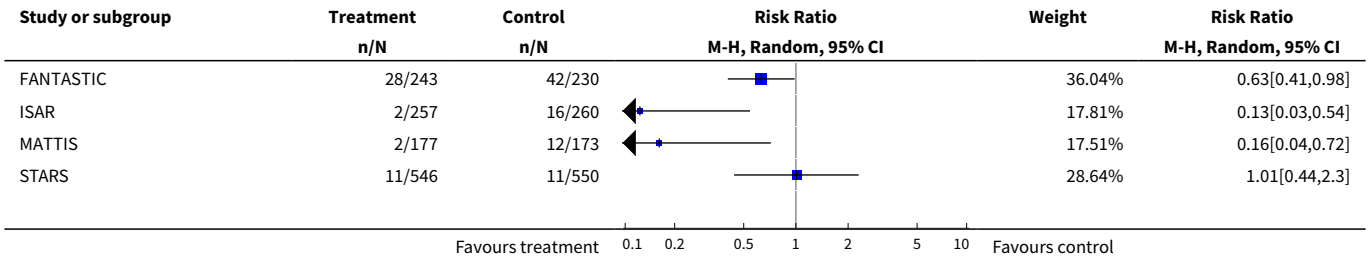

## Comparison 9. vascular access site bleeding

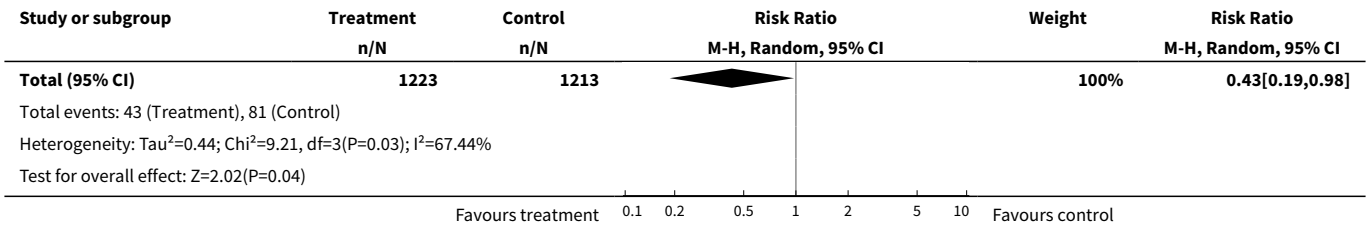
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 local bleeding complications (total) | 4 | 2436 | Risk Ratio (M-H, Random, 95% CI) | 0.41 [0.19, 0.88] |
| 2 vascular access site bleeding ( no ecchymosis) | 4 | 2436 | Risk Ratio (M-H, Random, 95% CI) | 0.43 [0.19, 0.98] |
| 3 total Jadad score > 3 | 3 | 1340 | Risk Ratio (M-H, Random, 95% CI) | 0.27 [0.09, 0.77] |

### Analysis 9.1. Comparison 9 vascular access site bleeding, Outcome 1 local bleeding complications (total).

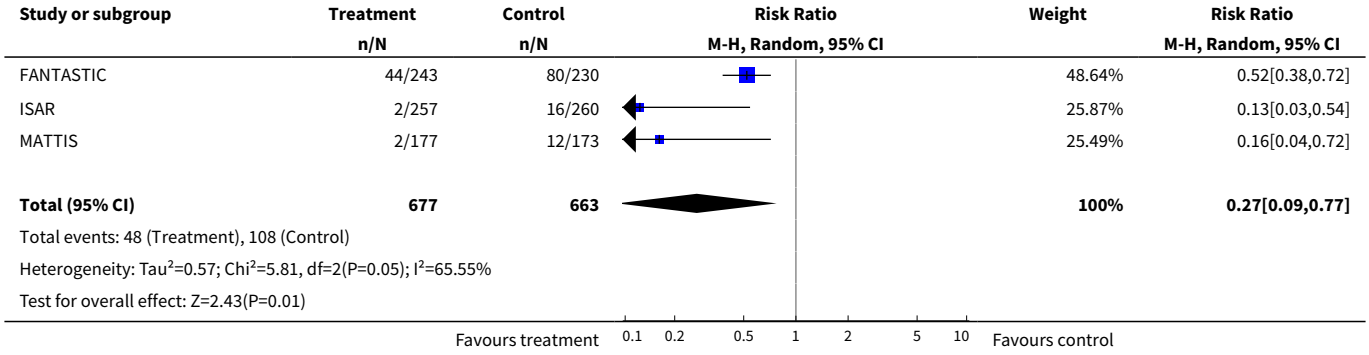



### Analysis 9.2. Comparison 9 vascular access site bleeding, Outcome 2 vascular access site bleeding ( no ecchymosis).





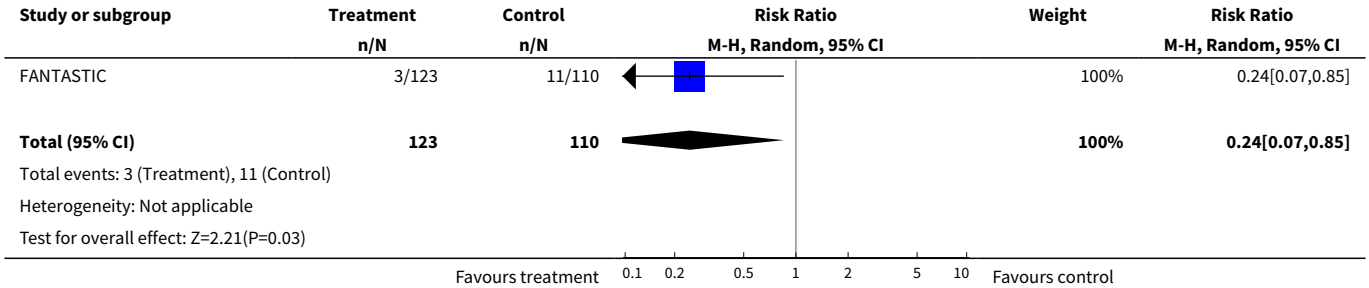

### Analysis 9.3. Comparison 9 vascular access site bleeding, Outcome 3 total Jadad score > 3.



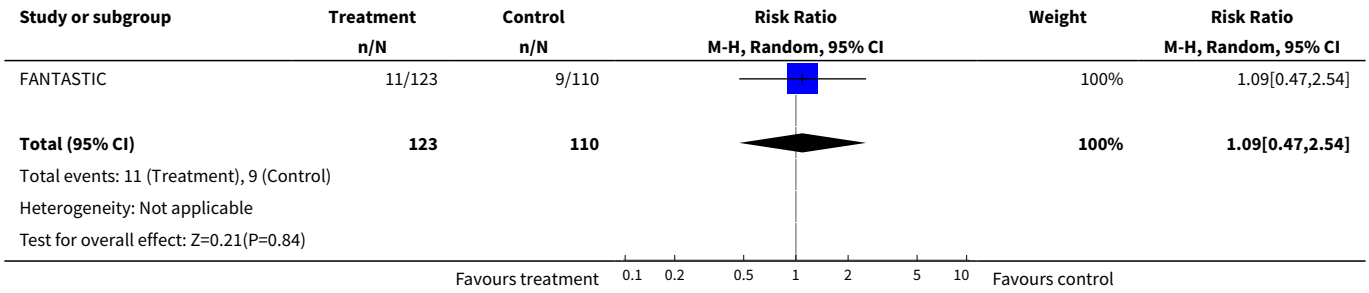

## Comparison 10. total primary outcome in elective versus unplanned stenting

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 elective stenting | 1 | 233 | Risk Ratio (M-H, Random, 95% CI) | 0.24 [0.07, 0.85] |
| 2 unplanned stenting | 1 | 233 | Risk Ratio (M-H, Random, 95% CI) | 1.09 [0.47, 2.54] |

### Analysis 10.1. Comparison 10 total primary outcome in elective versus unplanned stenting, Outcome 1 elective stenting.



**Analysis 10.2. Comparison 10 total primary outcome in elective versus unplanned stenting, Outcome 2 unplanned stenting.**




## F E E D B A C K

### From David Cundiff: September 2007

#### Summary

In this meta-analysis of noninferiority RCTs, the control group, ASA plus a vitamin K inhibitor, has never been shown to improve clinical outcomes for people with coronary stenting. Therefore, this meta-analysis cannot determine the effectiveness and safety of the use of ticlopidine plus aspirin after coronary stenting.

ASA plus warfarin may well do clinical harm due to rebound hypercoagulability [1-4] bleeding (3% rate of major hemorrhage the first month falling to 0.3% per month after the first year) [5] and hypercoagulability associated with initiation of vitamin K inhibition of vitamin K inhibition. A study from Italian anticoagulation clinics showed that, in 2111 patient-years on vitamin K inhibitors, 34/70 thromboses occurred within the first 90 days of treatment (OR of < or =90 days versus >90 = 20.6, CI 12.7-33.5; p <0.0001). These investigators found that the risk of thrombotic events when the INR is less than 1.5 is 7.6 times the risk when the INR is 2.0-2.99 in patients taking warfarin for various indications. [6]

The most relevant comparison would be between ASA and ASA plus ticlopidine. In this regard, Hall and colleagues published an informative RCT of ASA alone versus ASA + ticlopidine after stent placement, concluding, "At 1 month, there was no difference in the incidence of stent thrombosis or other clinical end points between the two poststent antiplatelet regimens." [7] Without evidence of efficacy of combination antiplatelet therapy over ASA alone, the 2-2.5% incidence of idiopathic bone marrow suppression and 0.8% incidence of severe neutropenia requiring prolonged hospitalization and antibiotics [7,8] make ticlopidine an unlikely candidate as part of the standard of care.

Since the safety of ticlopidine, regarding bone marrow suppression, is a major consideration in the overall risk/benefit ratio of ASA plus ticlopidine, large retrospective or prospective observational studies should have been included.

This Cochrane review references a 1998 RCT by Leon and colleagues justifying combination ASA plus ticlopidine thromboprophylaxis: "This regimen, now representing the gold standard after coronary stenting, is considered to be effective in reducing both the thrombotic occlusion of the stented vessel (and the associated clinical events) and the hemorrhagic and peripheral vascular complications." [9 ] The Leon trial comparing ASA alone, ASA plus ticlopidine and ASA plus warfarin had a peculiar arrangement of endpoints. Data relating to the primary endpoint, a composite of (1) death, (2) revascularization of the target lesion, (3) angiographically evident thrombosis, and (4) myocardial infarction within 30 days favored ASA plus ticlopidine (ASA alone =20/557 versus ASA plus ticlopidine =3/546, P < 0.001). The secondary endpoints were (1) procedure related myocardial infarction, (2) hemorrhagic complications, (3) vascular surgical complications, (4) neutropenia or thrombocytopenia, and (5) cerebrovascular accident. ASA plus ticlopidine caused more hemorrhagic complications (P < 0.001) and vascular surgical complications (P < 0.02) compared with the ASA alone. Indeed, when all primary and secondary clinical events combined are compared, ASA alone has a borderline statistical advantage (ASA alone 51/557 versus ASA plus ticlopidine 70/546, RR 0.69, 0.47 - 1.00). Leon and colleagues biased the interpretation of this RCT to favor ticlopidine plus ASA.

Consequently, the conclusion of this Cochrane review, "Ticlopidine plus aspirin after coronary stenting is effective in reducing the risk of the revascularization, non fatal myocardial infarction and bleeding complications when compared with oral anticoagulants" is not justified.

The review should be updated to reflect the late thrombosis risks of drug eluting stents [10] and that electively done percutaneous coronary interventions (angioplasties with or without stents) are evidence based not to improve clinical outcomes. [11] In this regard, it is notable that all deaths in the ASA plus ticlopidine group of this review (6/1223) were procedure complication related.

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**Reply**

The aim of the review was to compare ASA plus ticlopidine versus ASA plus vitamin K antagonists after coronary stenting and not the efficacy and safety of ASA plus ticlopidine per se. The review included trials performed mostly in the 1990s with bare metal stents and mostly after elective stents. Dual antiplatelet treatment seemed at least as effective as ASA plus vitamin K antagonists. Since then dual antiplatelet treatment with ASA plus ticlopidine or clopidogrel has become the standard treatment after coronary stenting. The comparison of ASA alone versus dual antiplatelet agents would entail an entirely different and new meta-analysis.

The meta-analysis of ASA plus ticlopidine versus ASA plus vitamin K antagonists should probably be considered historical as nowadays the relevant comparison would be the effectiveness and safety of ASA plus ticlopidine versus ASA plus clopidogrel after coronary stenting and thus, again, an entirely different question. Moreover nowadays drug-eluting stents should be considered as well primary angioplasty with stenting and therefore a different and new meta-analysis would be required. The original authorship team is no longer active and consequently not currently in a position to plan new meta-analyses.

**Contributors**

David Cundiff
Benilde Cosmi

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 29 November 2012 | Review declared as stable | This review is no longer being updated as the question is no longer relevant |

## HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 4, 2001

| Date | Event | Description |
|---|---|---|
| 9 September 2008 | Amended | Converted to new review format. |

| Date | Event | Description |
|---|---|---|
| 11 August 2001 | New citation required and conclusions have changed | Substantive amendment |

## CONTRIBUTIONS OF AUTHORS

All co-reviewers were active in the design of the review and in providing critical revisions of the manuscript. B. Cosmi arbitrated on study inclusion where necessary. B. Cosmi originated and was primarily responsible for planning and carrying out the review and was the principal author.

## DECLARATIONS OF INTEREST

There is no known conflict of interest.

## SOURCES OF SUPPORT

### Internal sources

- University of Bologna, Italy.
- S. Orsola-Malpighi Hospital, Bologna, Italy.
- Ospedale Maggiore, Bologna, Italy.

### External sources

- No sources of support supplied

## NOTES

This review is no longer being updated as the clinical question is out of date and other comparisons are now more clinically relevant.

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Stents; Administration, Oral; Anticoagulants [therapeutic use]; Aspirin [*therapeutic use]; Coronary Thrombosis [etiology] [*prevention & control]; Drug Therapy, Combination; Fibrinolytic Agents [*therapeutic use]; Platelet Aggregation Inhibitors [*therapeutic use]; Randomized Controlled Trials as Topic; Ticlopidine [*therapeutic use]

### MeSH check words

Humans