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Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease (Review)

Squizzato A, Keller T, Romualdi E, Middeldorp S

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[Intervention Review]

Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease

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ABSTRACT

Background

Aspirin is the prophylactic antiplatelet drug of choice for people with cardiovascular disease. Adding a second antiplatelet drug to aspirin may produce additional benefit for those at high risk and those with established cardiovascular disease.

Objectives

To quantify the benefit and harm of adding clopidogrel to standard long-term aspirin therapy for preventing cardiovascular events in people at high risk of cardiovascular disease and those with established cardiovascular disease.

Search methods

The searches have been updated: CENTRAL (Issue 3 2009), MEDLINE (2002 to September 2009) and EMBASE (2002 to September 2009).

Selection criteria

All randomized controlled trials comparing long term use of aspirin plus clopidogrel with aspirin plus placebo or aspirin alone in patients with coronary disease, ischemic cerebrovascular disease, peripheral arterial disease, or at high risk of atherothrombotic disease were included.

Data collection and analysis

Data on mortality, non-fatal myocardial infarction, non-fatal stroke, unstable angina, heart failure, revascularizations, major and minor bleeding, and all adverse events were collected. The overall treatment effect was estimated by the pooled odds ratio (OR) with 95% confidence interval (CI) using a fixed-effect model (Mantel-Haenszel).

Main results

No new studies were identified from the updated searches. A total of two RCTs were found: the CHARISMA and the CURE study. The CURE study enrolled only patients with a recent non-ST segment elevation acute coronary syndrome. The use of clopidogrel plus aspirin, compared with placebo plus aspirin, was associated with a lower risk of cardiovascular events (OR: 0.87, 95% CI 0.81 to 0.94; P<0.01) and a higher risk of major bleeding (OR 1.34, 95% CI 1.14 to 1.57; P<0.01). Overall, we would expect 13 cardiovascular events to be prevented for every 1000 patients treated with the combination, but 6 major bleeds would be caused. In the CURE trial, for every 1000 people treated, 23 events would be avoided and 10 major bleeds would be caused. In the CHARISMA trial, for every 1000 people treated, 5 cardiovascular events would be avoided and 3 major bleeds would be caused.

Authors' conclusions

The available evidence demonstrates that the use of clopidogrel plus aspirin is associated with a reduction in the risk of cardiovascular events and an increased risk of bleeding compared with aspirin alone. Only in patients with acute non-ST coronary syndrome benefits outweigh harms.

PLAIN LANGUAGE SUMMARY

Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease

Low-dose aspirin as antiplatelet therapy is still the drug of choice for preventing cardiovascular events, but the protection aspirin gives to people at high risk of cardiovascular events is only relatively modest. This review of 28,165 people in two trials where clopidogrel was given in addition to antiplatelet treatment found that in patients with acute coronary syndromes the benefit - a reduction in cardiovascular events - outweighs the harm of major bleeding. However, clopidogrel plus aspirin has no clear positive risk-benefit profile in people at high risk of cardiovascular events (multiple atherothrombotic risk factors) or in people with established cardiovascular disease (known coronary disease, ischemic cerebrovascular disease or peripheral arterial disease) but not presenting with an acute coronary syndrome, and the combination should not be prescribed routinely to prevent cardiovascular disease.

BACKGROUND

Description of the condition

Cardiovascular disease is a leading cause of mortality and morbidity worldwide. An estimated 17 million people die of cardiovascular disease each year (WHO 2003). Primary and secondary prophylaxis aims to modify major risk factors. Antiplatelet therapy improves the survival of patients with manifest cardiovascular disease (Patrono 2001).

Aspirin (acetyl salicylic acid) as antiplatelet therapy is the drug of choice, due to its good cost effectiveness profile (Gaspoz 2002). Based on a recent meta-analysis, the Antithrombotic Trialists' Collaboration (ATC) concluded that aspirin is protective in most patients at risk of cardiovascular events. In this analysis, patients at risk were those with acute myocardial infarction or ischemic stroke, unstable or stable angina, previous myocardial infarction, stroke or cerebral ischemia, peripheral arterial disease or atrial fibrillation (ATC 2002). Although the relative risk reduction of death, myocardial infarction and stroke in these patients was approximately 20% (ATC 2002), the protection with antiplatelet therapy in patients with a high risk of cardiovascular disease remains unsatisfactory in absolute terms. Moreover, low compliance and adverse effects limit the cost effectiveness of aspirin alone (Morant 2003). Adding a second antiplatelet drug to aspirin may produce additional benefits in some clinical circumstances (ATC 2002). New antiplatelet drugs and preventive strategies have been developed and studied. Previously published reviews and protocols in *The Cochrane Library* discuss both the importance of antiplatelet drugs and their limits in the prevention of cardiovascular disease, mainly in peripheral artery disease (Cosmi 2004; Dorffler-Melly 2003a; Dorffler-Melly 2003b; Dorffler-Melly 2005; Hankey 2004; Robless 2007; Robless 2004; Van de Laar 2005).

Description of the intervention

The combination treatment of clopidogrel plus aspirin could be a potential strategy to reduce cardiovascular disease. The antiplatelet drug clopidogrel, a thienopyridine derivative, has been compared with aspirin (CAPRIE 1996) and combined with aspirin (CREDO 2002; CURE 2001) and demonstrated a good safety profile in these studies. In addition, as confirmed by a systematic review by the UK National Institute for Health and Clinical Excellence (NICE), it was suggested that people with non-ST segment elevation acute coronary syndrome benefit from aspirin in combination with clopidogrel compared to treatment with aspirin alone (NICE 2004). A recent Health and Technology Assessment (HTA) economic evaluation and systematic review of clopidogrel in combination with aspirin for the treatment of non-ST segment elevation acute coronary syndromes confirmed the clinical and cost effectiveness of the combination therapy (HTA 2004). Given that the antiplatelet effect is consistent in different populations, any age, sex and risk subgroups could derive benefit from the combination therapy.

Adverse effects

Besides bleeding associated with combined antiplatelet use, thienopyridine-induced neutropenia is a major concern (Hankey 2004). Clopidogrel is the preferred thienopyridine, because it has a good safety profile. However, although the risk is lower compared to other thienopyridines, neutropenia has been described during clopidogrel use (CAPRIE 1996). Indeed, the US Food and Drugs Administration found 37 cases of clopidogrel-associated thrombotic thrombocytopenic purpura (TTP) between 1998 and 2002. TTP occurs usually within 2 weeks of drug initiation, and has a high mortality if not treated promptly (Zakarija 2004).

The aim of this systematic review (an update of a Cochrane review, Squizzato A, Keller T, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD005158) is to assess the effects of the combination of clopidogrel and aspirin compared with aspirin alone in the primary and secondary prevention of cardiovascular disease.

OBJECTIVES

1. To quantify the potential benefit of adding clopidogrel to long-term aspirin therapy for preventing acute myocardial infarction, ischemic stroke and vascular deaths in people at high risk of cardiovascular disease (multiple atherothrombotic risk factors) and in people with established cardiovascular disease (known coronary disease, ischemic cerebrovascular disease and peripheral arterial disease)

2. To quantify the potential harm of the combined therapy in terms of bleeding (major and minor bleeding, blood transfusion, hemorrhagic stroke or gastric bleeding) and adverse effects (i.e. renal failure, TTP, neutropenia, low platelets, gastric complaints and diarrhea)

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials comparing use of aspirin plus clopidogrel with aspirin plus placebo or aspirin alone, with follow-up > 30 days.

Types of participants

Studies were included if participants had known coronary disease, ischemic cerebrovascular disease, peripheral arterial disease, or were at high risk of atherothrombotic disease.

Types of interventions

Aspirin plus clopidogrel versus aspirin plus placebo or aspirin alone. No other platelet aggregation inhibitors as co-intervention were accepted.

Types of outcome measures

Primary

All cardiovascular events.

Secondary

Mortality from myocardial infarction.
Non-fatal myocardial infarction.
Unstable angina.
Heart failure.
Mortality from ischemic stroke.
Non-fatal ischemic stroke.
Revascularization procedures.
Mortality from cardiovascular causes.
All-cause mortality.
Major bleeding (hemorrhagic stroke, gastric bleeding, any bleeding requiring blood transfusion, any bleeding causing a hemoglobin level drop of > 2 mg/dL, or hospitalization).
Minor bleeding.

All adverse events (i.e. renal failure, thrombotic thrombocytopenic purpura (TTP), neutropenia, low platelets, gastric complaints, diarrhea, skin rash)

Search methods for identification of studies

Electronic searches

The Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (Issue 3 2009), MEDLINE (2002 to September 2009) and EMBASE (2002 to September 2009) were searched. MEDLINE and EMBASE have been systematically searched centrally for RCTs, or possible RCTS, and these have been added to CENTRAL. Because of this we searched MEDLINE and EMBASE only from 2002. No language restrictions were applied.

The search strategies used previously (Appendix 2) were updated for the search in 2009 (Appendix 1).

A standard RCT filter (Dickersin 1994) was used in the MEDLINE search.

Searching other resources

We performed an extensive manual search, checking of references from original articles and pertinent reviews. In addition we searched websites for recent or ongoing trials (www.epi.bris.ac.uk/cochrane/cardi.html, www.cardiosource.com, www.clinicaltrial.gov, www.controlled-trials.com).

We searched (electronic) databases and aimed to identify as many systematic reviews and meta analysis as possible. Studies were identified using the Database of Abstracts of Reviews of Effects (DARE) on *The Cochrane Library*.

Data collection and analysis

Study selection

Two review authors (TK and AS in the first version and AS and ER in this updated version) independently selected potentially eligible references from the search. The references were rejected if it could be determined from the title and/or abstract that the study was not suitable for inclusion in this review. The full text of the study was obtained when an article could not be excluded with certainty. Excluded studies were compared and any disagreement was solved through discussion between the reviewers.

Risk of bias assessment

We assessed the risk of bias in the included studies according to the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). We scored each of the following points as 'yes', 'no', or 'unclear' (where 'yes' indicates that the study is less open to bias) and report them in a 'Risk of bias' table.

(1) Method of randomisation (selection bias)

Methods of randomisation using date of birth, date of admission, hospital numbers, or alternation are not appropriate because they do not allow each study participant to have the same chance of receiving each intervention.

(2) Concealment of allocation (indication bias)

Adequate measures to conceal allocations are central randomisation; serially numbered, opaque, sealed envelopes; or other descriptions with convincing concealment.

(3) Blinding of investigators and patients (performance bias)

(4) Blinding of outcome assessment (detection bias)

(5) Adequate follow up (attrition bias)

Attrition bias refers to systematic differences between the comparison groups in the loss of participants from the study. We will carefully check the reporting of withdrawals, dropouts, protocol deviations, and losses to follow up. It is adequate when more than 90% of the patients have completed follow up and when reasons for withdrawals, dropouts, protocol deviations, and losses to follow up are clearly reported.

(6) Other possible bias

Based on these criteria, we divided studies into the following three categories:

A - all quality criteria met: low risk of bias;

B - one or more of the quality criteria only partly met: moderate risk of bias;

C - one or more criteria not met: high risk of bias.

To avoid selection bias, we did not reject any study because of methodological characteristics or any subjective quality criteria, except non-randomised studies. However, we planned to examine differences in study methods in sensitivity analyses.

Data extraction

Data were independently extracted using a predefined extraction form. A consensus meeting was used to deal with differences in the extracted data. No combined endpoints were extracted.

Authors were contacted for additional unpublished data. Data were extracted for all groups and subgroups together: coronary disease with and without drug-eluting stent (DES) or non-DES, ischemic cerebrovascular disease, peripheral arterial disease, or patients at high risk of atherothrombotic disease.

The following data were extracted:

General information: published/unpublished, title, authors, source, country, year of publication, duplicate publications.

Trial characteristics: design, duration, randomization (and method), allocation concealment (and method), blinding (outcome assessors), checking of blinding.

Intervention: loading dose, dosage, duration of treatment.

Participants: exclusion criteria, total number and number in comparison groups, gender/age, similarity of groups at baseline, withdrawals/losses to follow-up.

Outcome: mortality from myocardial infarction, non-fatal myocardial infarction, unstable angina, heart failure, mortality from stroke, non fatal stroke, revascularizations, all-cause mortality, major bleeding (hemorrhagic stroke, gastric bleeding, any bleeding requiring blood transfusion, any bleeding causing haemoglobin level drop of > 2 mg/dL), minor bleeding, all adverse events (i.e. renal failure, TTP, neutropenia, low platelets, gastric complains, diarrhea, skin rash).

'All cardiovascular events' was calculated by summing available secondary outcomes (fatal myocardial infarction, non-fatal myocardial infarction, unstable angina, heart failure, fatal ischemic stroke, non-fatal ischemic stroke, mortality from cardiovascular causes other than myocardial infarction and ischemic stroke) for each trial. Any trial definition of 'all cardiovascular events' was not taken in to account and no data were extracted. Revascularization procedures were excluded from the primary outcome to reduce the potential for bias. Many episodes of acute coronary events would have been followed by revascularization, leading to double counting of outcomes.

Data analysis

Data were analysed with RevMan version 4.2.2. Quantitative analysis of outcome was based on an intention-to-treat principle. The measure of effect for each study was the odds ratio (OR) with 95% confidence interval (CI). The overall treatment effect was estimated by the pooled OR with 95% CI using a fixed-effect model (Mantel-Haentzel). Each test for significance was two-tailed. Funnel plots were used to assess for evidence of publication bias (Egger 1997). Sensitivity analysis was used to take into account the influence of study quality. The main value of this review is in examining whether long-term administration of clopidogrel has a consistency of effect across all patients, but subgroup analyses were performed to assess the benefit in particular predefined subgroups. People with peripheral arterial disease have already been the subject of several Cochrane systematic reviews (Dorffler-Melly 2003a; Dorffler-Melly 2003b; Dorffler-Melly 2005; Robless 2007; Robless 2004).

Heterogeneity

We assessed heterogeneity with the Mantel-Haentszel chi-square test and I^2 test (Higgins 2003). For the first method trial data was considered to be heterogeneous if P<0.10, for the second method an I^2 value < 30% indicates mild heterogeneity, 30% to 50% moderate heterogeneity and >50% severe heterogeneity. In case of significant heterogeneity, an attempt was made to explain the differences based types of participants and study design difference.

RESULTS

Description of studies

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

Our updated search found 5047 references. We excluded 4798 references because they were not RCTs, were duplicates or investigated different topics. From abstracts, we excluded 55 references because a non-eligible intervention was tested, 129 references because a non-eligible population was tested and 35 references because only data on acute administration was available (< 30 days). Two references were for two ongoing studies. We retrieved the remaining 28 full text papers for inspection. Of these, 15 were excluded (three because no clinical endpoints were reported (two reported data on the same population); three because only data in the first 30 days were available; four because clopidogrel and placebo were administered for less than 30 days; one because it was a comparison of 1 month and 6 months of clopidogrel; four (reporting one trial) because clopidogrel was administered for 1 month in the aspirin-alone group). Further information of these excluded studies are given in the section Characteristics of excluded studies. Of the remaining 13 publications, one was a reference for FASTER 2007 (previously an ongoing study) which has been excluded because data were not available in the manuscript and the authors did not provide additional information. One was an additional reference for the excluded study CARESS 2005. Therefore, a total of 11 references reporting 2 studies was included (CHARISMA 2006; CURE 2001; Characteristics of included studies. Additionally, three ongoing trials, which were potentially eligible, were also identified from a search of online trial registers, giving a total of five ongoing studies (Characteristics of ongoing studies).

In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study

a total of 15,603 people at high risk for a cardiovascular event were randomized either to clopidogrel (75 mg per daily) plus low-dose aspirin (75 to 162 mg per day) or to placebo plus low-dose aspirin (CHARISMA 2006). In the clopidogrel plus aspirin and in the placebo plus aspirin group, these are the baseline characteristics, respectively: median age and range, 64.0 (39.0-95-0) and 64.0 (45.0-93.0); gender, 29.7% and 29.8% female; ethnicity, 80.4% and 79.9% White, 9.9% and 10.7% Hispanic, 5.0% and 5.0% Asian, 3.2% and 3.0% Black, 1.5% and 1.4% other. The trial was multicenter, including th following countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Mexico, The Netherlands, Norway, Poland, Portugal, Russia, Spain, South Africa, Sweden, Switzerland, Turkey, United Kingdom, United States. People were eligible for the trial if they were 45 years of age or older and had one of the following conditions: multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease, or documented symptomatic peripheral arterial disease. After a median of 28 months of follow-up, a predefined primary efficacy endpoint was composed including: the first occurrence of myocardial infarction, stroke (of any cause), or death from cardiovascular causes (including hemorrhage). The principal secondary efficacy endpoint was a composite of first occurrence of the primary endpoint, or hospitalization for unstable angina, a transient ischemic attack, or a revascularization procedure (coronary, cerebral, peripheral). The primary safety endpoint was severe bleeding, according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition, which includes fatal bleeding and intracranial hemorrhage, or bleeding that caused hemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention (GUSTO 1993). Both primary efficacy and primary safety endpoints were not significantly in favour of any treatment.

In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study a total of 12,562 people with a non-ST-segment-elevation acute coronary syndrome were randomized to receive either clopidogrel (a loading dose, 300 mg orally, followed by 75 mg daily) or placebo plus aspirin (recommended dose 75-325 mg) (CURE 2001). In the clopidogrel plus aspirin and in the placebo plus aspirin group, these are the baseline characteristics, respectively: mean age, 64.2 ± 11.3 and 64.2 ± 11.3; gender, 38.7% and 38.3% female; no data are available for ethnicity. The trial was multicenter, including th following countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Mexico, The Netherlands, New Zealand, Norway, Poland, Portugal, South Africa, Spain, Sweden, Switzerland, United Kingdom, United States. After a mean follow-up of 9 months, a predefined primary endpoint was composed including: death from cardiovascular causes, non-fatal acute myocardial infarction, or stroke (ischemic and hemorrhagic). A secondary combined endpoint was a composite of the primary endpoint and refractory ischemia. The safety endpoint of bleeding was defined as life threatening, severe (requiring two or more units of blood transfusions), or minor. Eight additional reports of the original CURE study were retrieved by the search. A specific benefit was found for clopidogrel, mainly due to a decreased risk of non-fatal myocardial infarction. However, no beneficial effect of clopidogrel was seen on several other outcomes, including fatal myocardial infarction and cardiovascular death. Minor, major and specific bleedings such as gastric bleeding or bleeding requiring transfusion of more than two units of blood, occurred more often in the clopidogrel group compared to placebo (a statistically significant difference).

All authors were contacted, but none provided additional data. Only the CHARISMA study randomized people without evidence of cardiovascular disease, but separate findings for these primary patients were not presented and could not be obtained from the trialists; consequently a comparison between efficacy of treatment in primary versus secondary prevention cannot be made.

Risk of bias in included studies

The CHARISMA and the CURE studies were both double blind, placebo controlled, randomized controlled trials. The study protocol was published in advance, before the end of the study. Based on the previously described criteria of quality assessment, we marked these studies as A, indicating that all quality criteria were met and that the data extracted from these studies have a low risk of bias. Both studies were funded by the pharmaceutical companies who developed and sell clopidogrel.

Effects of interventions

Data from two trials with a total of 28,165 people were available. The primary outcome in the CURE study was the sum of the following outcomes: fatal myocardial infarction, non-fatal myocardial infarction, unstable angina, fatal ischemic stroke and non-fatal ischemic stroke. The primary outcome in the CHARISMA study was the sum of the following outcomes: non-fatal myocardial infarction, non-fatal ischemic stroke and mortality from all cardiovascular causes.

The CURE trial, confined to people with acute non-ST segment coronary syndromes, showed definite evidence of benefit from treatment (all cardiovascular events: OR 0.84, 95% CI 0.77 to 0.93) (Analysis 1.1) and an increase in major bleeding (OR 1.39, 95% CI 1.14 to 1.70) (Analysis 2.1). The number needed to treat to avoid one cardiovascular event was 43, and the number needed to treat to cause one major bleed was 99. For every 1000 people treated for an average of 9 months, 23 events would be avoided and 10 major bleeds would be caused.

In the CHARISMA trial, which randomized people at high cardiovascular risk defined either in terms of pre-existing cardiovascular diseases or risk factors, the effects of treatment were less marked and were consistent with the play of chance (OR 0.92, 95% CI 0.81 to 1.04) (Analysis 1.1). There was only weak evidence of an increase in major bleeding (OR 1.25 (0.97 to 1.63)) (Analysis 2.1). The number needed to treat to avoid 1 cardiovascular event was 194, and the number needed to treat to cause 1 major bleed was 300. For every 1000 people treated for an average of 28 months, 5 cardiovascular events would be avoided and 3 major bleeds would be caused.

The pooled findings showed that, compared with aspirin alone, clopidogrel plus aspirin was associated with a small reduction in the risk of having a cardiovascular event during long-term follow-up (more than 30 days; minimum 6 months, maximum 28 months) (OR: 0.87, 95% CI 0.81 to 0.94; P < 0.01) (Analysis 1.1). In absolute terms, out of 1000 people treated with clopidogrel plus aspirin, 101 people had a cardiovascular event, compared with 114 people treated with aspirin alone (risk difference: 1.3%, 95% CI 1% to 2%).

A significant increase in bleeding was seen in people treated with clopidogrel plus aspirin. Compared with aspirin alone, the risk of having a major bleeding during 1 year of treatment was 34% higher in the clopidogrel plus aspirin group (OR 1.34, 95% CI 1.14 to 1.57; P < 0.01) (Analysis 2.1) with an absolute excess of 6 per 1000 patients treated with the combination for 1 year (25 versus 19, risk difference 0.6%, 95% CI 0% to 1%).

Overall, we would expect 13 cardiovascular events to be prevented for every 1000 people treated with clopidogrel plus aspirin but 6 major bleeds would be caused.

DISCUSSION

This systematic review of RCTs on the effect of long-term (>30 days) administration of clopidogrel plus low dose aspirin compared with long-term low dose aspirin alone for preventing cardiovascular disease in patients at high risk revealed 10 publications of two original RCTs. In these trials a benefit of clopidogrel was reported based on composite predefined endpoints only in the CURE study, but with an increased risk of major and minor bleedings. After extracting relevant clinical outcomes we combined these components in an overall endpoint of all cardiovascular events (as defined previously). We showed that the findings were consistent between the two trials conducted on different clinical groups with an overall beneficial effect of long-term clopidogrel plus aspirin but this was also associated with a significant increased risk of major bleeding.

For a correct interpretation of these data, some comments are necessary. Several single secondary outcomes were not available in the published papers, and could not be obtained from the trial investigators. This means that the overall treatment effect may be estimated with bias as published results from particular outcomes may be correlated with the size of the effect. For this reason we decided to report only the primary outcome (all cardiovascular events) and the main safety outcome (major bleeding). For the primary outcome, as reported above, available outcomes combined are similar but not identical: for CHARISMA, unstable angina data were not available, and fatal events were reported differently. Combined endpoints should always be interpreted with caution. For example, in the CURE study the potential beneficial effect of clopidogrel plus aspirin on non-fatal myocardial infarction is not extended to fatal myocardial infarction, unstable angina or cardiovascular death, although the risk for heart failure was somewhat diminished.

Offsetting the beneficial antithrombotic effect of clopidogrel is the clear increased risk of major and minor bleeding that has been demonstrated during long-term use of clopidogrel plus aspirin compared with aspirin alone in both clinical groups. The CHARISMA study investigated a population of high risk people for atherothrombotic disease with or without evidence of cardiovascular disease, which is exactly the overall and subgroup types of patients we planned to analyse. Unfortunately, only a few secondary outcomes were reported and available data on subgroup populations (i.e. people with coronary disease with and without DES or non-DES, ischemic cerebrovascular disease, peripheral arterial disease, or with established cardiovascular disease, multiple atherothrombotic risk factors, or those at high risk) were insufficient to derive secondary outcomes in this review or to conduct meaningful subgroup analyses. The authors told us that they are not allowed to provide CHARISMA data without Sanofi-Aventis permission.

The CURE study enrolled patients with a recent non-ST segment elevation acute coronary syndrome, and showed strong evidence of benefit for the primary combined outcome of cardiovascular events. By contrast, the CHARISMA study showed a non-significant reduction of the combination therapy compared with aspirin alone (OR 0.92, 95% CI 0.81 to 1.04), suggesting insufficient evidence to support the use of treatment with clopidogrel plus aspirin in non-acute patients at high risk of cardiovascular disease. Indeed, when the absolute treatment effects are examined in the CHARISMA trial, the events avoided and the major bleeding caused are quite similar.

Data from the CURE study suggest that the main benefit of combination therapy is in the initial period. Therefore, it is probable that clopidogrel in combination with ASA was associated with a even smaller reduction in the risk of having a cardiovascular event during long term follow-up to an average of 9 months. Given that we excluded trials with less than 30 days of treatment, a definitive

conclusion on the early effects of treatment and the optimal duration of treatment are not possible. In an update to our review we will include such trials in order to compare short term and long term treatment effects as an explicit objective in acute coronary syndromes.

In a CURE sub-group analysis (CURE 2001), the author reported data between 30 days and 1 year after randomization. The exclusion of patients who had an event in the first 30 days may have undermined the balance achieved by randomization in the groups. For this reason, these data are potentially biased and any interpretation is difficult. However, the National Institute of Health and Clinical Excellence (NICE 2004), has issued guidance based on the CURE trial findings for health professionals in England stating that 12 months treatment with clopidogrel plus aspirin is cost-effective in patients with non-ST segment acute coronary syndromes despite the increased risk of bleeding.

We identified five ongoing RCTs that potentially fit with our inclusion/exclusion criteria. Both included studies were funded by the pharmaceutical companies who developed and sell clopidogrel. This is a potential limitation and, therefore, data should be interpreted with caution. Both Sanofi-Aventis and Bristol-Myers Squibb did not provide us with additional information. Ongoing studies will increase the available evidence, but mainly for specific subgroups of people at high risk of cardiovascular disease because of clear evidence of pre-existing atherothrombotic disease (ischemic cerebrovascular disease, peripheral artery disease, coronary disease).

Based on the available evidence, we can demonstrate a small, statistically non-significant beneficial effect of adding clopidogrel to long-term administration of aspirin, but a significantly increased risk of bleeding, in people at high risk of atherothrombotic disease without evidence of cardiovascular disease, and in people with evidence of cardiovascular disease. In acute coronary syndrome the picture is clearer, with evidence of benefits outweighing major bleeding events. However, it is unclear whether the beneficial effect is largely due to early post-acute event combination therapy and is smaller in the long term. Future studies will provide additional data to assess whether specific subgroups (most notably patients with coronary disease who have undergone percutaneous coronary intervention) may benefit from long-term combined antiplatelet therapy with clopidogrel and aspirin.

AUTHORS' CONCLUSIONS

Implications for practice

Given the available evidence and until new data are published, clinicians should not add clopidogrel to standard long-term aspirin therapy for preventing cardiovascular disease in people at high risk of cardiovascular disease and in those with established cardiovascular disease. In patients with acute non-ST coronary syndromes, there is evidence of benefit outweighing harms caused by major bleeding and combination treatment should be considered.

Implications for research

From a public health perspective, given the high prevalence of atherothrombosis, even a small benefit may be desirable. The results from ongoing trials will clarify the real risk-benefit of long-term clopidogrel and aspirin combination therapy versus aspirin alone in specific subgroup populations (ischemic cerebrovascular disease, peripheral arterial disease and coronary surgery). If a real benefit exists in any subgroup, data from ongoing trials will suggest the optimal duration of combination therapy, and which thrombotic and hemorrhagic variables can modify the risk-benefit profile. Moreover, as other CHARISMA data are available, the publication of all thrombotic and bleeding outcomes and subgroup analyses are advisable to better understand on which type of people the research should be focused. At this time, it is not advisable to start new RCTs until new data from the ongoing studies are available. Finally, forthcoming trials should uniformly present outcomes, in order to avoid many of the problems we have experienced in being unable to get the relevant data and to permit easier systematic reviewing of the RCTs.

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REFERENCES

References to studies included in this review

CHARISMA 2006 *{published data only}*

* Bhatt DL, Fox KAA, Hacke W, Berger PB, Black HR, Boden WE, et al.Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *New England Journal of Medicine* 2006;**354**:1706–17.

Steinhubl SR, Bhatt DL, Brennen DM, Montalescot G, Hankey GJ, et al.Aspirin prevent cardiovascular disease: the association aspirin dose and clopidogrel with thrombosis and bleeding. *Ann Intern Med* 2009;**150**:379–86.

CURE 2001 *{published data only}*

Anand SS, Xie CC, Mehta S, Franzosi MG, Joyner C, Chrolavicius S, et al.Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. *Journal of the American College of Cardiology* 2005;**46**:1845–51.

BuDaj A, Yusuf S, Mehta SR, Fox KA, Tognoni G, Zhao F, et al.Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. *Circulation* 2002;**106**(13):1622–6.

Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, et al.Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation* 2004;**110**(10): 1202–8.

Lewis BS, Mehta SR, Fox KAA, Halon DA, Zhao F, Peters RJG, et al.Benefit of clopidogrel according to timing of percutaneous coronary intervention in patients with acute coronary syndromes: further results from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *American Heart Journal* 2005;**150**:1177–84.

Mahoney EM, Mehta S, Yuan Y, Jackson J, Chen R, Gabriel S, et al.Long-term cost-effectiveness of early and sustained clopidogrel therapy for up to 1 year in patients undergoing percutaneous coronary intervention after presenting with acute coronary syndromes without ST-segment elevation. *American Heart Journal* 2006;**151**:219–27.

Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al.Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;**358**:527–33.

Peters RJG, Mehta SR, Fox KAA, Zhao F, Lewis BS, Kopecky SL, et al.Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: Observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 2003;**108**(14):1682–7.

Yusuf S, Mehta SR, Zhao F, Gersh BJ, Commerford PJ, Blumenthal M, et al.Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation* 2003; **107**(7):966–72.

* Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al.Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *New England Journal of Medicine* 2001; **345**:494–502.

References to studies excluded from this review

Akbulut 2004 *{published data only}*

Akbulut M, Ozbay Z, Karaca I, Ilkay E, Gundogdu O, Arslan N. The effect of long-term clopidogrel use on neointimal formation after percutaneous coronary intervention. *Coronary Artery Disease* 2004;**15**:347–52.

Azar 2006 *{published data only}*

Azar RR, Kassab R, Zoghbi A, Aboujaoudé S, El-Osta H, Ghorra P, et al.Effects of clopidogrel on soluble CD40 ligand and on high-sensitivity C-reactive protein in patients ith stable coronary artery disease. *American Heart Journal* 2006;**151**:521.e1–e4.

CARESS 2005 *{published data only}*

Dittrich R, Ritter MA, Kaps M, Siebler M, Lees K, Larrue V, Nabavi DG, Ringelstein BE, Markus HS, Droste DW. The use of embolic signal detection in multicenter trials to evaluate antiplatelet efficacy signal analysis and quality control mechanisms in the CARESS (clopidogrel and aspirin reduction emboli symptomatic carotid stenosis). *Stroke* 2006;**37**:1065–69.

* Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al.Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection. The clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis (CARESS) trial. *Circulation* 2005;**111**:2233–40.

Cassar 2005 *{published data only}*

Cassar K, Ford I, Greaves M, Bachoo P, Brittenden J. Randomized clinical trial of the antiplatelet effects of aspirin-clopidogrel combination versus aspirin alone after low limb angioplasty. *British Journal of Surgery* 2005;**92**: 159–65.

CLARITY-TIMI 28 2005 *{published data only}*

Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, et al.Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *New England Journal of Medicine* 2005;**352**:1179–89.

COMMIT 2005 *{published data only}*

COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;**366**:1607–21.

CREDO 2002 *{published data only}*

Kelly RV, Hsu A, Topol E, Steinhubl S. The influence of body mass index on outcomes and the benefit of antiplatelet

therapy following percutaneous coronary intervention. *The Journal of Invasive Cardiology* 2006;**18**:115–119.
Mukherjee D, Topol EJ, Moliterno DJ, Brennan DM, Ziada K, Cho L, et al.Extracardiac vascular disease and effectiveness of sustained clopidogrel treatment. *Heart* 2006;**92**:49–51.
Saw J, Topol EJ, Steinhubl SR, Brennan D, Berger PB, Moliterno DJ, et al.Comparison of long-term usefulness of clopidogrel therapy after the first percutaneous coronary intervention or coronary artery bypass grafting versus that after the second or repeat intervention. *American Journal of Cardiology* 2004;**94**:623.
* Steinhubl SR, Berger PB, Mann JTIII, Fry ET, DeLago A, Wilmer C, et al.Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;**288**:2411–20.

FASTER 2007 ***{published data only}***
Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk, Buchan AM, for the FASTER Investigators. Fast assessment of stroke and transient ischemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol* 2007;**6**:961–9.

Jagroop 2004 ***{published data only}***
Jagroop IA, Matsagas MI, Geroulakos G, Mikhailidis DP. The effect of clopidogrel, aspirin and both antiplatelet drugs on platelet function in patients with peripheral arterial disease. *Platelets* 2004;**15**:117–25.

Pekdemir 2003 ***{published data only}***
Pekdemir H, Cin VG, Camsari A, Cicek D, Akkus NM, Doven O, et al.A comparison of 1-month and 6-month clopidogrel therapy on clinical and angiographic outcome after stent implantation. *Heart & Vessels* 2003;**18**(3):123–9.

Steinhubl 2006 ***{published data only}***
Steinhubl SR, Berger PB, Brennan DM, Topol EJ, for the CREDO Investigators. Optimal timing for the initiation of pre-treatment with 300 mg clopidogrel before percutaneous coronary intervention. *Journal of the American College of Cardiology* 2006;**47**:939–43.

Xydakis 2004 ***{published data only}***
Xydakis D, Papadogiannakis A, Sfakianaki M, Vakouti E, Papachristoforou K. The combination of clopidogrel and acetylsalicylic acid inhibits more effective the platelet activation in haemodialysis patients with acute coronary syndromes and high C reactive protein. 41st Congress of the European Renal Association. European Dialysis and Transplantation Association. Lisbon, Portugal, May 15-18, 2004. 2004:355.

Zhao 2003 ***{published data only}***
Zhao L, Fletcher S, Weaver C, Leonardi-Bee J, May J, Fox S, et al.The effects of three anti-platelet drugs (aspirin, clopidogrel, dipyridamole) given singly or together on platelet and leucocyte function in healthy subjects and patients with previous ischemic stroke. *Journal of Thrombosis & Haemostasis* 2003;**1**(Suppl 1):Abstract number: P1010.

References to ongoing studies

ASAP-CABG ***{published data only (unpublished sought but not used)}***
Aspirin and Plavix following coronary artery bypass grafting. *http://www.clinicaltrial.gov*.

CASCADE ***{published data only (unpublished sought but not used)}***
Randomized control trial of clopidogrel after surgery for coronary artery disease. http://www.clinicaltrial.gov..

CASPAR ***{published data only (unpublished sought but not used)}***
Clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease. http://www.clinicaltrial.gov.

MIRROR Trial ***{published data only (unpublished sought but not used)}***
Follow-up management of peripheral arterial intervention with clopidogrel. http://www.clinicaltrial.gov.

SPS3 ***{published data only (unpublished sought but not used)}***
Secondary prevention of small subcortical strokes trial. http://www.controlled-trials.com.

Additional references

ATC 2002
Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trails of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients.. *British Medical Journal* 2002;**324**: 71–86.

CAPRIE 1996
CAPRIE Steering Committee. A randomised, blinded, trial of clopidrogel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–39.

Cosmi 2004
Cosmi B, Rubboli A, Castelvetri C, Milandri M. Ticlopidine versus oral anticoagulation for coronary stenting. *Cochrane Database of Systematic Reviews* 2004, Issue 2.

Dickersin 1994
Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**:1286–91.

Dorffler-Melly 2003a
Dorffler-Melly J, Buller HR, Koopman MM, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database of Systematic Reviews* 2003, Issue 3. [DOI: 10.1002/14651858.CD000535]

Dorffler-Melly 2003b
Dorffler-Melly J, Buller HR, Koopman MM, Prins MH. Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery. *Cochrane Database of Systematic Reviews* 2003, Issue 2. [DOI: 10.1002/14651858.CD000536]

Dorffler-Melly 2005
Dorffler-Melly J, Koopman MMW, Prins MH, Buller HR. Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion following peripheral endovascular treatment. *Cochrane Database of Systematic Reviews* 2005, Issue 1. [DOI: 10.1002/14651858.CD002071.pub2]

Egger 1997
Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34.

Gaspoz 2002
Gaspoz JM, Coxson PG, Goldman PA, Williams LW, Kuntz KM, Hunink MGM, et al.Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease.. *New England Journal of Medicine* 2002;**346**: 1800–6.

GUSTO 1993
The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *New England Journal of Medicine* 1993;**329**:673–82.

Hankey 2004
Hankey GJ, Sudlow CLM, Dunbabin DW. Thienopyridine derivates (ticlopidine, clopidogrel) versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. *Cochrane Database of Systematic Reviews* 2004, Issue 2.

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**: 557–60.

Higgins 2008
Higgins JPT, Altman DG (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 (updated September 2008). The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

HTA 2004
Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M. Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation. *Health Technology Assessment* 2004;**40**:1–56.

Morant 2003
Morant SV, McMahon AD, Cleland JGF, Davey PG, MacDonald TM. Cardiovascular prophylaxis with aspirin: costs of supply and management of upper gastrointestinal and renal toxicity. *British Journal of Clinical Pharmacology* 2003;**57**:188–98.

NICE 2004
Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, et al.A rapid and systematic review on clinical effectiveness and cost-effectiveness of clopidogrel used in combination with aspirin compared to aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes (ACS) (Assessment Report). National Institute for Clinical Excellence on behalf of the National Health Service, UK 2004; Vol. available at http://www.nice.org.uk/.

Patrono 2001
Patrono C, Coller B, Dalen JE, Fitzgerald GA, Fuster V, Gent M, et al.Platelet-active drugs: the relationships among dose, effectiveness, and side effects. *Chest* 2001;**119**(1 Suppl):39S–63S.

Robless 2004
Robless P, Mikhailidis D, Stansby G. Cilostazol for peripheral arterial disease. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD001272]

Robless 2007
Robless P, Mikhailidis D, Stansby GP. Antiplatelet agents for intermittent claudication. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD003748.pub2]

Van de Laar 2005
Van de Laar FA, Akkermans RP, De Grauw WJC, Hovens MMC. Adenosin-diphosphate (ADP) receptor antagonists (clopidogrel, ticlopidine) for the prevention of cardiovascular disease in type 2 diabetes mellitus (Protocol). *Cochrane Database of Systematic Reviews* 2005, (3):CD005449.

WHO 2003
WHO Global Burden Disease Estimates. *World Health Reports*. Geneva: World Health Organization, 2003.

Zakarija 2004
Zakarija A, Bandarenko N, Pandey DK, Auerbach A, Raisch DW, Kim B, et al.Clopidogrel-associated TTP: an update of pharmacovigilance efforts conducted by independent researchers, pharmaceutical suppliers, and the Food and Drug Administration. *Stroke* 2004;**35**:533–7.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

CHARISMA 2006

Methods	Randomized controlled trial.
Participants	15,603 people at high risk of a cardiovascular event (both primary and secondary prevention)
Interventions	Clopidogrel plus aspirin (n = 7802) versus placebo plus aspirin (n = 7801)
Outcomes	Primary efficacy endpoint: composite of the first occurrence of myocardial infarction, stroke (of any cause), or death from cardiovascular causes (including hemorrhage). Principal secondary efficacy endpoint: composite of first occurrence of the primary endpoint, or hospitalization for unstable angina, a transient ischemic attack, or a revascularization procedure (coronary, cerebral, peripheral). Primary safety endpoint: severe bleeding, which includes fatal bleeding and intracranial hemorrhage, or bleeding that caused hemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	No	Pharmaceutical industry funded

CURE 2001

Methods	Randomized controlled trial.
Participants	12,562 people with acute non-ST elevation coronary syndrome.
Interventions	Clopidogrel plus aspirin (n = 6259) versus placebo plus aspirin (n = 6303)

Outcomes	First primary outcome: composite of death from cardiovascular causes, non-fatal myocardial infarction, or stroke. Second primary outcome: composite of the first primary outcome or refractory ischemia. Secondary outcomes: severe ischemia, heart failure and the need for revascularization. Safety-related outcomes: bleeding complications, which were categorized as life-threatening, major (two or more units of blood), or minor
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	No	Pharmaceutical industry funded

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

Study	Reason for exclusion
Akbulut 2004	No clinical end-points were reported.
Azar 2006	No clinical end-points were reported.
CARESS 2005	Clopidogrel and placebo was administered for only 7 days.
Cassar 2005	Only data for the first 30 days of therapy administration.
CLARITY-TIMI 28 2005	Only data for the first 30 days of combined clopidogrel-aspirin administration
COMMIT 2005	Clopidogrel and placebo was administered only until discharge or for up to 4 weeks in hospital
CREDO 2002	The placebo-allocated group received clopidogrel for 1 month after PCI

(*Continued*)

FASTER 2007	No single clinical endpoints were reported in the published manuscript. Investigators did not provide additional data
Jagroop 2004	No clinical endpoints were reported.
Pekdemir 2003	Comparison of 1 month versus 6 months of clopidogrel after PCI
Steinhubl 2006	Only data for the first 28 days of therapy administration and on different clopidogrel loading doses
Xydakis 2004	Clopidogrel and placebo were administered for only 5 days.
Zhao 2003	Clopidogrel and placebo were administered for only 2 weeks.

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

ASAP-CABG

Trial name or title	ASpirin And Plavix following Coronary Artery Bypass Grafting
Methods	Randomised controlled trial
Participants	Patients undergoing coronary artery bypass graft with or without the use of cardiopulmonary bypass
Interventions	Clopidogrel 75 mg daily plus aspirin 81 mg compared with aspirin 81 mg alone
Outcomes	Graft stenosis, TIMI major and minor bleeding. 52 days follow-up
Starting date	July 2010
Contact information	http://www.clinicaltrial.gov
Notes	Estimated study completion date: July 2012

CASCADE

Trial name or title	Clopidogrel After Surgery for Coronary Artery Disease (CASCADE trial)
Methods	Randomised controlled trial
Participants	Patients undergoing primary multi-vessel coronary artery bypass graft with at least two saphenous vein grafts, with or without the use of cardiopulmonary bypass
Interventions	Clopidogrel 75 mg daily plus aspirin compared with aspirin alone

CASCADE (*Continued*)

Outcomes	Vein graft intimal area, vein graft angiographic patency, incidence of major adverse coronary events, major bleeding events. One year follow-up
Starting date	2005
Contact information	http://www.clinicaltrial.gov
Notes	According to http://www.clinicaltrial.gov, the trial was completed on June 25th, 2010. We will make reasonable attempts to obtain information from published data and include them in the next update

CASPAR

Trial name or title	Clopidogrel and Acetyl Salicylic Acid in Bypass Surgery for Peripheral ARterial Disease (CASPAR trial)
Methods	Randomised controlled trial
Participants	Patients receiving a below knee bypass graft for the treatment of peripheral arterial disease
Interventions	Clopidogrel 75 mg daily versus placebo (on a background of aspirin 75-100 mg daily)
Outcomes	Primary patency, limb salvage and survival, cardiovascular death, myocardial infarction, stroke, any amputation above the ankle, ankle brachial pressure index (ABPI) changes from baseline
Starting date	September 2004
Contact information	http://www.controlled-trials.com
Notes	According to http://www.clinicaltrial.gov, the trial was completed on September 17th, 2009. We will make reasonable attempts to obtain information from published data and include them in the next update

MIRROR Trial

Trial name or title	MIRROR trial: Follow-up Management of Peripheral Arterial Intervention With Clopidogrel
Methods	Randomised controlled trial
Participants	Peripheral arterial disease which requires intervention.
Interventions	Clopidogrel or placebo.
Outcomes	Platelet activation, the effect on macro- and microcirculation will be assessed as well as clinical endpoints
Starting date	2005
Contact information	http://www.clinicaltrial.gov

MIRROR Trial (*Continued*)

Notes	Estimated study completion date: October 2008 (last update in http://www.clinicaltrial.gov was in 2007)

SPS3

Trial name or title	Secondary Prevention of Small Subcortical Strokes (SPS3 trial)
Methods	Randomised controlled trial
Participants	One of the lacunar stroke clinical syndromes lasting > 24 hours within the past 6 months
Interventions	Clopidogrel plus aspirin versus aspirin alone.
Outcomes	Recurrent strokes and reduction in cognition (no other endpoints reported)
Starting date	2003
Contact information	http://www.clinicaltrial.gov
Notes	Estimated study completion date: June 2011

DATA AND ANALYSES

Comparison 1. PRIMARY OUTCOME

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cardiovascular events	2	28165	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.81, 0.94]

Comparison 2. MAIN SAFETY OUTCOME

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Major bleeding	2	28165	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [1.14, 1.57]

WHAT'S NEW

Last assessed as up-to-date: 27 February 2010.

Date	Event	Description
9 August 2010	New citation required but conclusions have not changed	New author added.
9 August 2010	New search has been performed	Searches have been re-run to September 2009. No new studies were included in this update

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 3, 2007

Date	Event	Description
8 September 2008	Amended	Converted to new review format.
9 March 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Squizzato

Guarantor of the review. Conception and design of the study. Data collection. Analysis and interpretation of data, providing a clinical perspective. Drafting the review. Final approval of the version to be published

Keller

Conception and design of the study. Data collection. Analysis and interpretation of data. Revising the review critically for important intellectual content. Final approval of the version to be published

Romualdi

Data collection. Analysis and interpretation of data, providing a methodological perspective. Revising the review critically for important intellectual content. Final approval of the version to be published

Middeldorp

Conception, design and coordination of the study. Analysis and interpretation of data, providing a methodological perspective. Revising the review critically for important intellectual content. Final approval of the version to be published

DECLARATIONS OF INTEREST

Keller was involved as sub-investigator in the CHARISMA study

SOURCES OF SUPPORT

Internal sources

- Academic Medical Center, Netherlands.
- University of Insubria, Italy.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Aspirin [adverse effects; *therapeutic use]; Cardiovascular Diseases [*prevention & control]; Drug Therapy, Combination [adverse effects; methods]; Platelet Aggregation Inhibitors [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Ticlopidine [adverse effects; *analogs & derivatives; therapeutic use]

MeSH check words

Humans