Drug Class Review

Newer Antiplatelet Agents

Final Update 2 Report

June 2011

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

Shading indicates new information for Update 2.

STRUCTURED ABSTRACT

Purpose

We compared the effectiveness and harms of clopidogrel, ticlopidine, extended-release dipyridamole and aspirin and prasugrel in adults with acute coronary syndromes or coronary revascularization (stenting, bypass grafting), ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease.

Data Sources

We searched Ovid MEDLINE®, the Cochrane Database of Systematic Reviews®, and the Cochrane Central Register of Controlled Trials® and Database of Abstracts of Reviews of Effects through January 2011. We also hand searched reference lists, US Food and Drug Administration medical and statistical reviews, and dossiers submitted by pharmaceutical companies.

Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to standard Drug Effectiveness Review Project review methods.

Results and Conclusions

High-strength evidence indicated that in coronary revascularization, prasugrel reduces target-vessel revascularization more than clopidogrel at 15 months, while moderate-strength evidence indicated that there was more major bleeding with prasugrel. Evidence was moderate strength that the use of clopidogrel for 6 months after coronary revascularization resulted in lower risk of revascularization compared with 1 month, with no increase in bleeding (moderate strength). The benefit lessened after 8 and 12 months and bleeding risk gradually increased (moderate to low strength). In patients with acute coronary syndrome who are managed medically, there was moderate-strength evidence of no significant difference in reduction of mortality out to at least 12 months, significantly fewer myocardial infarctions, and increased major bleeding between clopidogrel plus aspirin compared with aspirin alone.

Following stroke or transient ischemic attack, high-strength evidence indicated that extended-release dipyridamole plus aspirin did not meet criteria for being noninferior to clopidogrel for the primary outcome of recurrent stroke and had higher risks of major bleeding and withdrawals due to adverse events.

Evidence was insufficient to draw strong conclusions about the benefit-risk ratio of using a proton pump inhibitor for any patients taking clopidogrel.

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Published in a separate document.

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INTRODUCTION

Atherosclerosis often starts in late adolescence or early adulthood, although clinical manifestations typically occur years later. Statistics from 2008 indicate that approximately 82.6 million Americans have at least 1 type of cardiovascular disease including ischemic coronary heart disease, stroke, and/or peripheral arterial disease. An estimated 2200 Americans die of cardiovascular disease each day, an average of 1 death every 39 seconds. About 795 000 people will experience a new or recurrent stroke each year, meaning that on average, every 40 seconds someone in the United States has a cerebrovascular accident.[1]

Ischemic coronary heart disease varies in its presentation and includes stable angina, unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction. All of these presentations except stable angina are often referred to as acute coronary syndrome. Atherosclerotic cerebrovascular disease also varies in presentation from asymptomatic arterial stenosis (i.e., carotid stenosis), to transient ischemic attacks to thromboembolic stroke. Likewise, peripheral arterial disease may manifest as intermittent claudication of the lower extremity, although other presentations include arterial aneurysms, typically of the aorta, and renovascular disease. Some patients with peripheral arterial disease may not even experience any symptoms at all.

Although there are various approaches to secondary prevention of vascular disease, a principal component is the use of antiplatelet agents. Aspirin has been considered the standard agent for many years. Numerous studies have shown the efficacy of aspirin in reducing the occurrence of major cardiovascular events including death, recurrent myocardial infarction, recurrent angina, or progression to severe angina and nonfatal stroke. Various clinical practice guidelines have recently been published that provide current guidance and recommendations regarding the use of aspirin for antiplatelet therapy.[2-8] However, this Newer Antiplatelet Agents Update 2 Report does not address the role of aspirin as an antiplatelet agent.

Over the past decade or more, newer antiplatelet agents have come to the forefront as adjuncts to or substitutes for aspirin in many clinical situations. However, the role of individual antiplatelet agents relative to each other is still evolving. The objective of this study is to review evidence on the comparative effectiveness/efficacy and comparative harms of the newer antiplatelet agents listed in Table 1 (aspirin 25 mg /extended-release dipyridamole 200 mg [Aggrenox®] and the thienopyridines, clopidogrel [Plavix®], prasugrel [Effient®], and ticlopidine [Ticlid®]) for treatment of adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease, and to determine if there are any subgroups of patients based on demographics, socioeconomic status, other medications, or comorbidities for which any included drugs are more effective or associated with fewer harms.

Table 1 below lists the interventions that are included in this report. Appendix B lists boxed warnings for the interventions.

Table 1. Included interventions

Drug	Trade name	Labeled indications	Dosing
Aspirin/ extended-release dipyridamole 25 mg/200 mg	Aggrenox®	To reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis	One capsule bid
Clopidogrel[a]	Plavix®	**ACS** • NSTEMI, including patients managed medically and those managed with coronary revascularization • STEMI **Recent MI, recent stroke or established PAD** To reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death	**ACS** NSTEMI: 300 mg loading dose, continue at 75 mg qd in combination with ASA 75 to 325 mg qd STEMI: 75 mg qd in combination with 75-325 mg ASA with or without thrombolytics; Plavix® may be initiated with or without a loading dose **Recent MI, recent stroke or established PAD** 75 mg qd **CYP2C19 Poor Metabolizers** Appropriate dose regimen has not been established **Use with PPI** An appropriate dosing regimen has not yet been established
Prasugrel	Effient™	To reduce the rate of thrombotic cardiovascular events in patients with ACS, managed with percutaneous coronary intervention as follows: • Patients with unstable angina or NSTEMI • Patients with STEMI when managed with primary or delayed percutaneous coronary intervention	60 mg loading dose then 10 mg qd; patients taking Effient™ should also take ASA 75-325 mg; patients <60 kg should lower maintenance dose to 5 mg
Ticlopidine[a]	Generic only	To reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke Adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation	**Stroke** 250 mg bid **Coronary artery stenting** 250 mg bid with ASA for 30 days of therapy following stent implantation

[a] As monotherapy or in combination with aspirin.
Abbreviations: ACS, acute coronary syndrome; ASA, Aspirin; bid, twice daily; bid, twice daily; MI, myocardial infarction; NSTEMI, non-ST Segment Elevation Myocardial Infarction, PAD, peripheral arterial disease; PPI, proton pump inhibitor; qd, once daily; STEMI, ST Segment Elevation Myocardial Infarction.

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. They focus on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with careful formulation of research questions. The goal is to select questions that are important to patients and clinicians then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are preferred over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat is the number of patients who would need be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, well-conducted cohort designs are preferred for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to whether results of *efficacy studies* can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid disease, meaning disease other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that are impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also

often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the "average" patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report, we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling a study as either an efficacy or an effectiveness study, although convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of study results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decisionmaking. Users of an

evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The goal of this report is to compare the effectiveness and harms of newer antiplatelet agents. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, outcomes of interest, and, based on these, eligibility criteria for studies. A draft of these questions and inclusion and exclusion criteria were posted on the Drug Effectiveness Review Project website for public comment. The draft was reviewed and revised by representatives of the organizations participating in the Drug Effectiveness Review Project. Revision took into consideration input from the public and from clinical advisors and the organizations' desire for the key questions to reflect populations, drugs, and outcome measures of interest to clinicians and patients.

When the scope of the second update was originally finalized in October of 2010, review included cilostazol, clopidogrel, ticlopidine, the fixed-dose combination product containing extended-release dipyridamole and aspirin, and prasugrel. However, after the review was underway, the organizations participating in the Drug Effectiveness Review Project decided to eliminate cilostazol. Cilostazol had not been selected as a drug of interest by the organizations participating in the Drug Effectiveness Review Project at either the time of the original review in 2005 or during the first update in 2006. For the current update, the participating organizations initially agreed to add cilostazol for the sake of completeness. But, ultimately, it was determined that the reviewer manpower required to evaluate the large volume of literature associated with adding cilostazol would exceed the funding allocated for this update and it was eliminated from the review. This is not to imply there is no role or no evidence available for cilostazol in this area. Readers are referred to the current treatment guidelines cited in the introduction. The following key questions and inclusion criteria reflect the aforementioned revision and were approved by the organizations participating in the Drug Effectiveness Review Project in January 2011 to guide the review for this report:

1. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in effectiveness?

2. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in harms?

3. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in effectiveness and harms based on duration of therapy?

4. Are there subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one antiplatelet agent is more effective or associated with fewer harms?

METHODS

Inclusion Criteria

Populations

- Acute coronary syndromes managed medically (only)
- Acute coronary syndromes managed with coronary revascularization via stenting or bypass grafting
- Prior ischemic stroke or transient ischemic attack
- Symptomatic peripheral vascular disease

Drugs

- Extended-release dipyridamole and aspirin (Aggrenox®)
- Clopidogrel[a] (Plavix®)
- Prasugrel (Effient™)
- Ticlopidine[a] (generic products only)

[a] As monotherapy or in combination with aspirin.

Effectiveness Outcomes

- Mortality (all-cause and cardiovascular)
- Cardiovascular events (fatal or nonfatal myocardial infarction, fatal or nonfatal stroke)
- Invasive vascular procedure failure including the need for additional invasive vascular procedures

Harms Outcomes

- Overall adverse events reported
- Withdrawals due to adverse events
- Major adverse events (e.g. major bleeding)
- Specific adverse events or withdrawals due to specific adverse events (including, but not limited to, nonfatal extracranial bleeding, neutropenia, rash, etc.)

Study Designs

1. For effectiveness, controlled clinical trials and recent, good quality systematic reviews
2. For harms, controlled clinical trials and observational studies (cohort and case-control studies)

Literature Search

To identify articles relevant to each key question, we searched Medline (1994 to May 2006), Embase (1994 to May 2006), the Cochrane Central Register of Controlled Trials (Fall 2004 to May 2006), and reference lists of included review articles. In electronic searches, we combined terms for drug names, indications, and included study designs, all limited to human and English language (see Appendix C for complete search strategies). Pharmaceutical manufacturers were invited to submit dossiers. Aggrenox[9] and Clopidogrel[10] dossiers were received for the first version of this document. No dossier material was reviewed for the update. However, Boehringer Ingelheim Pharmaceuticals and Sanofi-aventis (on behalf of Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership) submitted comments on the draft of the updated report. All citations were imported into an electronic database (ProCite for Windows, Version 5.0.3.).

For Update 2, we searched Ovid MEDLINE® (1996 to December Week 4 2010), the Cochrane Database of Systematic Reviews® (2005 to December 2010), the Cochrane Central Register of Controlled Trials® (4th Quarter 2010), and Database of Abstracts of Reviews of Effects® (4th Quarter 2010) using included drugs, indications, and study designs as search terms (see Appendix C for complete search strategies). We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® X2, Thomson Reuters).

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion using the criteria below. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by both reviewers. Disagreements were resolved by consensus. Results published *only* in abstract form were not included because inadequate details were available for quality assessment.

We included English-language reports of randomized controlled trials that evaluated and included the newer antiplatelet agents (extended-release dipyridamole/aspirin, clopidogrel, ticlopidine, and prasugrel) in patients with acute coronary syndrome, stroke, transient ischemic attack, and symptomatic peripheral vascular disease, and that reported an included outcome. Included trials evaluated a newer antiplatelet agent compared with either another study antiplatelet agent or newer antiplatelet agent that met the inclusion criteria above.

To evaluate efficacy, we assessed controlled clinical trials. The validity of controlled trials depends on how they are designed. Properly randomized controlled trials are considered the

highest level of evidence for assessing efficacy. Clinical trials that are not randomized or blinded and those that have other methodological flaws are less reliable but are also discussed in the report.

Likewise, we excluded trials that compared an antiplatelet agent only to placebo because the acceptable standard of care today would more than likely (if clinically warranted and possible) include at least aspirin therapy. Lastly, only trials that specifically utilized Aggrenox® or their components together were included because the components of Aggrenox® are not interchangeable with the individual components of aspirin and immediate-release dipyridamole (Persantine®).

For many of the treatment outcomes, the newer antiplatelet agents were evaluated against some other standard of care, typically aspirin, rather than against another study antiplatelet agent. Although these trials provided indirect evidence regarding the comparative efficacy of these agents, they are not as useful as direct, head-to-head comparisons.

Clinical trials as well as observational cohort studies were included to evaluate rates of adverse events. Clinical trials typically either excluded patients who had experienced an adverse event on the therapy being evaluated or included a patient population where the risk of an adverse event was minimized in order to avoid a high dropout rate. Observational studies are a useful supplement to clinical trial data for adverse events because they may include a broader patient population with a large number of patients evaluated over a longer period of time. Many of the clinical trials of the newer antiplatelet agents included large patient populations with a long follow-up period, but not all were large or designed to rigorously evaluate adverse events. Only observational studies including more than 1000 patients with duration of *at least 1 year* or that focused on serious and rare adverse events were included in the assessment of adverse events. In order to evaluate the safety of the newer antiplatelet agents, we abstracted overall adverse effect reports, withdrawals due to adverse effects (a marker of more serious adverse events), serious adverse events reported (including mortality), and specific adverse effects or withdrawals due to specific adverse events (e.g., bleeding, neutropenia, diarrhea, rash).

Data Abstraction

The following data were abstracted from included trials: population characteristics (including sex, age, and ethnicity); eligibility; interventions (dose and duration); comparisons; numbers enrolled, withdrawn; lost to follow-up and analyzed; results for each relevant efficacy/effectiveness and harms outcomes; total withdrawals; withdrawals due to adverse events; and funding. We recorded intent-to-treat results when reported. If true intent-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intent-to-treat results. In cases where only per protocol results were reported, we calculated intent-to-treat results if the data for these calculations were available. Data abstraction was performed by 1 reviewer and independently checked by a second reviewer and differences were resolved by consensus.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria (see www.ohsu.edu/drugeffectiveness). These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom)

criteria.[11, 12] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intent-to-treat analysis. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others are only *possibly* valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist. A particular randomized trial might receive 2 different ratings, one for effectiveness and another for adverse events.

The criteria used to rate observational studies of adverse events reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair quality if they met 3 to 5 criteria, and poor quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality. We rated the internal validity based a clear statement of the questions(s); reporting of inclusion criteria; methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence; and details provided about included studies. Again, these studies were categorized as good when all criteria were met.

Two reviewers independently assessed each study and differences were resolved by consensus.

Grading the Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.[13] Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. For the purposes of this review, a rating of "indirect" was given to all aspirin-controlled trials. For rating of precision, we adopted the GRADE system's suggestion of downgrading evidence with a 95% confidence interval around the estimate of effect that includes both 1) no effect and (2) appreciable benefit or appreciable harm, using a threshold of 25% for both appreciable benefit and harm.

Table 2 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy, and harms of newer antiplatelet agents. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals. Two reviewers independently assessed each domain for each outcome and differences were resolved by consensus.

Among the many outcomes assessed in trials of newer antiplatelet agents, we focused on rating the strength of evidence for only a subset of 4 that the Drug Effectiveness Review Project participants judged to represent the most clinically important and reliable: all-cause mortality,

cardiovascular mortality, major bleeding, and withdrawals due to adverse events. We also rated the strength of the evidence for the following treatment- or population-specific outcomes: (1) neutropenia in trials including ticlopidine; (2) myocardial infarction in patients with acute coronary syndromes; (3) revascularization in patients undergoing stenting or bypass grafting; and (4) stroke recurrence in patients with a recent stroke or transient ischemic attack. Composite cardiovascular outcomes are very common in trials of antiplatelet agents. However, composite endpoints have been found to carry an inherent risk of misleading interpretation when they are comprised of component endpoints that have wide variance in both importance to patients and in contribution to the composite endpoint event rate.[14] For this reason, we considered composite endpoints to be of lower priority in this review and did not formally rate the strength of their results.

Table 2. Definitions of the grades of overall strength of evidence[15]

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated one antiplatelet against another provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data are the primary focus. Direct comparisons were preferred over indirect comparisons; similarly, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes.
In theory, trials that compare antiplatelet agents with other drug classes or with placebo can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily heterogeneity of trial populations, interventions, and outcomes assessment. Data from indirect comparisons are used to support direct comparisons, where they exist, and are used as the primary comparison where no direct comparisons exist. Indirect comparisons should be interpreted with caution.

Quantitative analyses were conducted using meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough that combining their results could be justified. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. When meta-analysis could not be performed, the data were summarized qualitatively. When the number of studies was sufficiently large to reliably estimate the tau-squared statistic, random effects models were used to estimate pooled effects.[16]

We generally set this number at 4 or more studies. When estimating pooled effects from a smaller number of studies, fixed-effects models were used.

The Q statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.[17, 18] Potential sources of heterogeneity were examined by analysis of subgroups of study design, study quality, patient population, and variation in interventions. All supplemental analyses were performed using Stats Direct statistical software (version 2.7.8, 3/15/2010).

Peer Review

We requested and received peer review of the report from 2 content experts. Their comments were reviewed and, where possible, incorporated into the final document. All comments and the authors' proposed actions were reviewed by representatives of the participating organizations of the Drug Effectiveness Review Project before finalization of the report. Names of peer reviewers for the Drug Effectiveness Review Project are listed at www.ohsu.edu/drugeffectiveness.

Public Comment

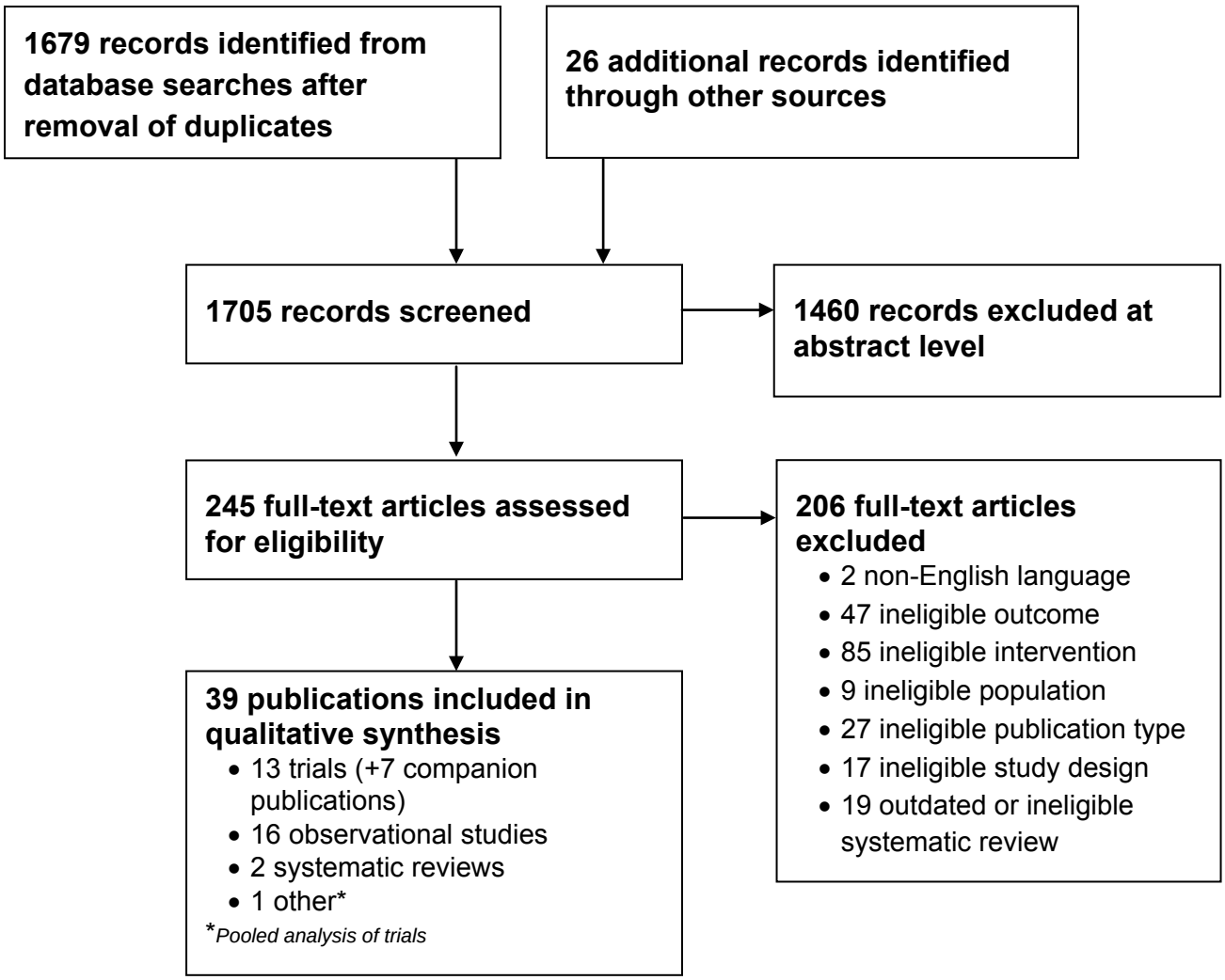
This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 3 pharmaceutical companies: Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb, and Eli Lilly and Company.

RESULTS

Overview

For update 2, literature searches identified 1705 citations. We received dossiers from 1 pharmaceutical manufacturer, Eli Lilly and Company. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 245citations. After reapplying the criteria for inclusion, we ultimately included 39 publications, representing 29 unique studies. See Appendix D for a list of excluded studies and reasons for exclusion at this stage. Figure 1 shows the flow of study selection for Update 2. Appendix E details the results of literature searches for studies included previously.

Figure 1. Results of literature search for Update 2[a]



[a] A modified PRISMA diagram was used.[19]

Key Question 1. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in effectiveness?

Summary of Findings

Direct evidence

- No head-to-head trials of newer antiplatelet agents for acute coronary syndrome managed medically only or peripheral vascular disease were identified.

Acute coronary syndrome managed with coronary revascularization via stenting or bypass grafting

- The TRITON-TIMI 38 trial provided moderate- to high-strength evidence that prasugrel is similar to clopidogrel for reduction of all-cause mortality and cardiovascular mortality at 15 months when used post percutaneous coronary intervention. It also provided high-strength evidence that prasugrel reduces the risk of target-vessel revascularization at 15 months.
- There was low-strength evidence of no significant difference between ticlopidine and clopidogrel in revascularization for periods up to 6 months. There was also low-strength evidence that the difference between ticlopidine and clopidogrel in cardiovascular mortality was not significant at 30 days.

Stroke or transient ischemic attack

- The PRoFESS trial provided high-strength evidence that extended-release dipyridamole plus aspirin failed to demonstrate noninferiority when compared with clopidogrel for the primary outcome of recurrent stroke and that there was no significant difference between extended-release dipyridamole plus aspirin and clopidogrel on the secondary outcomes of all-cause mortality and cardiovascular mortality.
- There was moderate-strength evidence of no significant difference between clopidogrel and ticlopidine in reduction of all-cause mortality, cardiovascular mortality, or cerebral infarction over 52 weeks.

Indirect evidence

Acute coronary syndrome managed medically

- There was moderate-strength evidence from CURE of no significant difference between clopidogrel plus aspirin compared with aspirin alone in reduction of all-cause mortality at 12 months, but there was a significantly greater reduction in myocardial infarction with clopidogrel plus aspirin.
- CURE and CHARISMA both found no significant advantage for clopidogrel plus aspirin over aspirin alone in reducing risk of cardiovascular mortality at 12 months (moderate strength) and 28 months (low strength).
- CAPRIE found no significant advantage for clopidogrel alone over aspirin alone in reducing risk of cardiovascular mortality at 22.8 months (low strength).

Stroke or transient ischemic attack

- Indirect evidence from aspirin-controlled trials of newer antiplatelet agents was consistent with direct evidence from head-to-head trials in suggesting no significant differences in effectiveness between extended-release dipyridamole plus aspirin and clopidogrel or between clopidogrel and ticlopidine.
- When taken immediately following transient ischemic attack or minor stroke, the use of clopidogrel in addition to aspirin did not significantly reduce the risk of stroke compared to aspirin alone. However, this result should be considered inconclusive as the FASTER trial was likely underpowered to detect a significant treatment difference.

Peripheral vascular disease

- In the peripheral arterial disease subgroup of the CAPRIE study, there was no significant difference between clopidogrel and aspirin in cardiovascular mortality. All-cause mortality and revascularization data were not reported separately for the peripheral arterial disease subgroup.
- Compared with aspirin alone, there was no significant benefit from dual therapy with clopidogrel plus aspirin in reducing all-cause mortality, cardiovascular mortality, or revascularization.

Detailed Assessment

Acute coronary syndrome managed medically

Direct evidence

No direct evidence was identified.

Indirect evidence

The Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events Trial (CURE)[20, 21] was a randomized, double blind, placebo-controlled trial of good quality that evaluated the early and long-term efficacy and safety of clopidogrel and aspirin. The trial included 12 562 patients hospitalized within 24 hours of the onset of chest pain, with a diagnosis of acute coronary syndrome, and without ST-segment elevation. Initial inclusion criteria allowed for patients > 60 years of age who had a history of coronary artery disease but no acute electrocardiogram changes. After the first 3000 patients were enrolled, only patients with myocardial necrosis or electrocardiogram changes (higher risk patients) were included in the study. The patients were randomized to clopidogrel (300 mg loading dose, 75 mg daily thereafter) plus aspirin or placebo plus aspirin for a mean of 9 months. The median dose of aspirin in both arms was 150 mg.[22] Patients enrolled in the CURE[21] trial were from centers that tended to favor a conservative approach to the treatment of acute coronary syndrome, so the usage rates of other modalities, such as angiography, percutaneous coronary intervention, and GP IIb/IIIa agents, were typically lower than the rates at many United States centers. The primary outcome was a composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or stroke (clopidogrel: 9.3% compared with placebo:11.4%; relative risk, 0.82; 95% CI, 0.73 to 0.90; $P<0.001$) or the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, stroke, or refractory ischemia (clopidogrel: 16.5% compared with placebo:18.8%, relative risk, 0.88; 95% CI, 0.81 to 0.95; $P<0.001$). The benefit of clopidogrel was observed within 24 hours after randomization in the primary outcome. In CURE,[21] clopidogrel/aspirin was compared with placebo/aspirin and there was no significant difference in cardiovascular deaths (5.1% compared with 5.5%; relative risk, 0.93; 95% CI, 0.80 to 1.10) or all-cause deaths (relative risk, 0.93; 95% CI, 0.81 to 1.07). The incidence of myocardial infarction for clopidogrel/aspirin compared with placebo/aspirin at 12 months was 5.2% compared with 6.7% (relative risk, 0.78; 95% CI, 0.68 to 0.90; $P<0.001$), which corresponds to a number needed to treat of 68. These component outcomes were all secondary endpoints and the study was not powered to detect a difference.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA)[13] trial was another randomized, double-blind, placebo-controlled trial of good quality. It compared the efficacy and safety of clopidogrel plus low-dose aspirin (75 mg-162 mg/day) with low-dose aspirin in patients at high risk for a cardiovascular event. This was mixed population trial including patients with multiple atherothrombotic risk factors (i.e. asymptomatic patients) and patients with established cardiovascular disease (i.e. symptomatic patients). Patients enrolled in the established cardiovascular group had either documented coronary disease (e.g., angina with documented multivessel coronary disease, history of multivessel percutaneous coronary intervention, history of multivessel coronary artery bypass graft surgery, myocardial infarction during previous 5 years), documented cerebrovascular disease (e.g., transient ischemic attack or ischemic stroke during previous 5 years), or documented symptomatic peripheral arterial disease (e.g., current intermittent claudication and ankle-brachial index ≤ 0.85, history of intermittent claudication, and previous intervention including amputation, peripheral bypass, or angioplasty), and were designated "symptomatic."

The CHARISMA[23] trial demonstrated no significant benefit with clopidogrel plus aspirin as compared with placebo plus aspirin in reducing the incidence of the primary endpoint of myocardial infarction, stroke, or death from cardiovascular causes in patients with stable cardiovascular disease or multiple cardiovascular risk factors (clopidogrel: 6.8% compared with placebo: 7.3%; relative risk, 0.93; 95% CI, 0.83 to 1.05; P=0.22). In the CHARISMA[23] trial, the subgroup that appeared to benefit from the therapy were the "symptomatic" group. In CHARISMA,[23] the authors stated that the cardiovascular mortality did not differ significantly between clopidogrel/aspirin and placebo/aspirin in the symptomatic subgroup, but actual figures were not reported. The asymptomatic subgroup appeared to have potentially worse outcomes. As with all subgroup analyses, these findings should be interpreted cautiously.

The Aspirin in Patients at Risk of Ischemic Events (CAPRIE)[24] study compared clopidogrel 75 mg to aspirin 325 mg daily for reducing the risk of future thrombotic events (myocardial infarction, stroke, or vascular death). Treatment with clopidogrel did not significantly reduce the risk of vascular death or death from any cause compared with treatment with aspirin. Three subsets of patients were enrolled (e.g., those with a history of recent myocardial infarction, recent ischemic stroke, or symptomatic peripheral arterial disease). In CAPRIE,[24] for the subgroup with myocardial infarction the relative risk for cardiovascular mortality was greater for clopidogrel compared with aspirin (relative risk, 1.16; 95% CI, 0.88 to 1.51; not significant).

Acute Coronary Syndrome Managed with Coronary Revascularization via Stenting or Bypass Grafting

Direct evidence

Prasugrel compared with clopidogrel

TRITON-TIMI 38[25] was a phase 3 trial that included 13 608 patients with moderate- to high-risk acute coronary syndromes (74% non-ST segment elevation myocardial infarction, 26% ST segment elevation myocardial infarction) who received percutaneous coronary interventions. It was a good-quality, multi-site, head-to-head trial and provided moderate- to high-strength evidence of no significant differences between prasugrel and clopidogrel in the most important effectiveness outcomes of all-cause mortality (hazard ratio, 0.95; 95% CI, 0.78 to 1.16; not

significant) and cardiovascular mortality (hazard ratio, 0.89; 95% CI, 0.70 to 1.12; not significant). However, as the study was not powered or designed to detect differences in these secondary outcomes, the results should be interpreted with caution. Despite the lack of power, it provided high-strength evidence of superiority of prasugrel over clopidogrel for prevention of target vessel revascularization post-percutaneous coronary intervention (2.5% compared with 3.7%; hazard ratio, 0.66; 95% CI, 0.54 to 0.81; $P<0.001$; absolute risk reduction, 1.2%; number needed to treat, 83). The primary efficacy outcome was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. All outcomes were assessed at 15 months. A post-hoc analysis of the ST-segment elevation myocardial infarction subgroup in TRITON-TIMI 38[26] reported Kaplan-Meier Hazard Ratios of all-cause mortality (hazard ratio, 0.76; 95% CI, 0.54 to 1.07), cardiovascular death (hazard ratio, 0.74; 95% CI, 0.50 to1.09), and target vessel revascularization (hazard ratio, 0.70; 95% CI, 0.46 to 1.06). Mean age was 61 years old and 26% were female and 92.5% were white. It compared prasugrel (60 mg load, followed by 10 mg daily) to clopidogrel (300 mg load, followed by 75 mg daily). Patients were followed to 15 months. Two other fair-quality head-to-head trials[27, 28] were smaller (n= 201 and n=905) and shorter (14 days and 30 days) studies to establish dose and had too few events to evaluate.

Ticlopidine compared with clopidogrel

Seven trials compared ticlopidine with clopidogrel in patients who had undergone placement of a coronary stent.[29, 30-34, 35, 37] Two included *only* patients with acute coronary syndrome.[29, 31] Patients enrolled in 3 other fair-quality trials included 50% or fewer patients with acute coronary syndrome.[30-34] An additional 2 studies were rated poor quality.[35, 37]

The good quality, 28-day, CLASSICS[29] trial was primarily a safety study evaluating ticlopidine in combination with aspirin compared with clopidogrel 75 mg (without loading dose) compared with clopidogrel 75 mg (with 300 mg loading dose) in combination with aspirin in 1020 patients following successful coronary stent procedure. Patient histories included previous myocardial infarction (36.3%), unstable angina (43.2%), and stable angina (55.8%). The mean age was 60 years and predominately male (77%). The primary endpoint consisted of major peripheral bleeding or complications, neutropenia or thrombocytopenia, or early discontinuation of study drug as the result of a noncardiac adverse event during the study-drug treatment period. Numerous secondary outcomes were evaluated in the CLASSICS[29] trial including major adverse clinical events defined as myocardial infarction (fatal and nonfatal), target lesion revascularization, and sudden death. All-cause mortality was not reported and there was a single cardiovascular death reported in the clopidogrel loading dose group. The relative risk of revascularization of ticlopidine compared with clopidogrel no load was 0.99 (95% CI, 0.06 to 15.69; not significant).

Di Pasquale, et al.[31] conducted a fair-quality double-blind, randomized, single-center trial comparing ticlopidine 500 mg daily to clopidogrel 75 mg daily in 428 patients hospitalized with a diagnosis of first episode of acute coronary syndrome. The diagnosis of acute coronary syndrome included patients with acute or rapidly worsening symptoms thought to be due to coronary artery disease as well as non-ST segment elevation myocardial infarction. All patients received aspirin 160 mg daily and GP IIb/IIIa infusion. During the 180 day follow-up, the relative risk of target vessel revascularization for ticlopidine compared to clopidogrel was 0.91 (95% CI, 0.62 to 1.33; not significant).

Three other studies were fair quality and included patients with stable or unstable angina or post myocardial infarction as the reason for their stent placement.[30-34] In a study with 4 weeks

of treatment, followed by 2.5 years of follow-up,[33] 700 patients who underwent successful stent implantation for any reason at a single-center received clopidogrel or ticlopidine. Over 28 months (24 months without treatment) the primary endpoint of cardiovascular mortality was significantly lower in patients assigned to receive ticlopidine compared to those taking clopidogrel (relative risk, 0.32; 95% CI, 0.15 to 0.69; number needed to treat, 20). In addition, all-cause mortality was lower with ticlopidine compared with clopidogrel (relative risk, 0.32; 95% CI, 0.15 to 0.66; number needed to treat, 18). Because treatment was not continued beyond 4 weeks, it is not clear how these results relate to results from other studies.

In an open-label trial in a broad population of 1016 patients with successful implantation of a stent in a native coronary artery or in a coronary artery bypass graft, cardiac death at 30 days occurred more frequently in the ticlopidine group but did not reach statistical significance (relative risk, 2.52; 95% CI, 0.67 to 9.46; not significant).[34] There was no difference in target vessel revascularization (relative risk, 0.95; 95% CI, 0.43 to 2.09; not significant). Ticlopidine and clopidogrel were given for only the first 2 weeks of follow-up in this study.

The study by Atmaca, et al[30] was from a single center that included 158 patients with stable angina pectoris and de novo lesions in large coronary arteries undergoing elective single vessel percutaneous transluminal coronary angioplasty with stenting. Follow-up was only 6 days and there was a nonsignficant increased rate in major clinical events (death, acute myocardial infarction, percutaneous coronary intervention, or bypass surgery) with ticlopidine compared with clopidogrel. Two additional studies were poor quality due to small sample size, lack of reporting the method for randomization, allocation concealment, and masking, or were unmasked.[35, 37] Both studies utilized doses of aspirin that are no longer used in clinical practice.

Indirect evidence

The active-control study performed by Hall, et al.[38] was an open-label, randomized trial comparing ticlopidine and aspirin with aspirin alone after stent implantation. The study was judged to be of poor quality.

Rupprecht, et al.[39] randomized patients to 1 of 3 groups: (1) ticlopidine; (2) ticlopidine plus aspirin 300 mg; or (3) aspirin 300 mg. The primary aim of the study was to assess the antiplatelet effects of these various regimens. In that regard, ticlopidine plus aspirin was superior in terms of platelet aggregation parameters and platelet activation markers compared with aspirin or ticlopidine alone. The study randomization was inadequate, allocation was not concealed nor was the outcome assessor masked, and the study was rated poor quality. Kayacioglu, et al.[40] was an open-label, randomized study of 60 patients who underwent coronary artery bypass graft surgery operation with a 6-month follow-up. It was rated poor because of unclear allocation concealment methods, unclear attrition, and small sample size. It also did not report all-cause mortality or cardiovascular mortality or major bleeding.

Stroke or Transient Ischemic Attack

Direct evidence

Three head-to-head trials provided moderate- to high-strength evidence of no significant differences between included antiplatelet agents in the most important effectiveness outcomes of all-cause mortality, cardiovascular mortality, and recurrent stroke.[41-43] The fixed-dose combination of aspirin 25 mg and extended-release dipyridamole 200 mg was compared with clopidogrel 75 mg in the Prevention Regimen for Effectively Avoiding Second Strokes

(PRoFESS) trial.[42] The PRoFESS trial was rated good quality and included 20 332 patients who were 66.1 years of age (mean), 64% male, and who had had an ischemic stroke within 90 days of study entry. Mean follow-up duration was 2.5 years. The PRoFESS trial was originally designed to test the superiority of the fixed-dose combination of extended-release dipyridamole plus aspirin, but the analysis plan was subsequently modified to include a sequential analysis, which first tested for the noninferiority of the fixed-dose combination of extended-release dipyridamole plus aspirin over clopidogrel. It was unclear when and why the analysis plan was modified. Similar rates of the primary outcome of recurrent stroke were found for the fixed-dose combination of extended-release dipyridamole plus aspirin compared with clopidogrel (9.0% compared with 8.8%; hazard ratio, 1.01; 95% CI, 0.92 to 1.11). However, because the upper limit of the confidence interval (1.11) fell slightly beyond the prespecified noninferiority margin of 1.075, no conclusions can be made about the relative effectiveness of the fixed-dose combination of extended-release dipyridamole plus aspirin compared with clopidogrel. Subgroup analyses found no significant differences between the fixed-dose combination of extended-release dipyridamole plus aspirin compared with clopidogrel in rates of recurrent stroke regardless of variation in history of stroke, stroke risk score, alcohol use, age, sex, ethnic group, obesity, status use, angiotensin converting enzyme inhibitor use, time since onset of qualifying stroke, Trial of Org 10172 in Acute Stroke Treatment criteria, diabetes, hypertension, or baseline systolic blood pressure. Rates of various secondary and tertiary outcomes were also similar for the fixed-dose combination of extended-release dipyridamole plus aspirin and clopidogrel, including all-cause mortality (7.3% compared with 7.4%; hazard ratio, 0.97; 95% CI, 0.87 to 1.07) and cardiovascular mortality (4.3% compared with 4.5%; hazard ratio; 0.94, 95% CI, 0.82 to 1.07). The only outcome for which the fixed-dose combination of extended-release dipyridamole plus aspirin demonstrated a significant advantage was in reducing the rate of new or worsening congestive heart failure (1.4% compared with 1.8%; hazard ratio, 0.78; 95% CI, 0.62 to 0.96).

Two fair-quality randomized controlled trials compared the effectiveness and harms of clopidogrel 75 mg and ticlopidine 200 mg in Japanese patients with prior stroke for 26 weeks[43] and 52 weeks.[41, 43] Together, these trials included 1869 patients who were 64 years of age and 71% male. Time from the most recent stroke was less than 4 weeks for 26.4% of patients, was between 4 and 12 weeks for 21.4%, and was over 12 weeks for the remaining 51.9%. When results of the 2 trials were combined, there was no significant difference in the rate of cerebral infarction between the clopidogrel (2.6%) and ticlopidine (2.5%) groups (hazard ratio, 0.92; 95% CI, 0.52 to 1.63).[43] Regarding all-cause mortality, only those deaths considered to be related to study medication were reported and there were only 2 in each treatment group (0.2% compared with 0.2%). There were no vascular deaths reported in either treatment group.

Indirect evidence

Indirect comparison meta-analysis

Just prior to publication of the head-to-head trials discussed above that compared the fixed-dose combination of aspirin 25 mg and extended-release dipyridamole 200 mg with clopidogrel 75 mg[42] and clopidogrel to ticlopidine,[41-43] results of an indirect network meta-analysis were released which suggested that the combination of aspirin and dipyridamole were the "most powerful antiplatelet regimen in the prevention of serious vascular events after transient ischemia attack or stroke."[44] The network meta-analysis included 24 trials involving 42 688 patients and found that for the Antiplatelet Trialists' Collaboration (APTC) composite endpoint of nonfatal

stroke, nonfatal myocardial infarction, and vascular death, rate of events was significantly lower for dipyridamole plus aspirin compared with thienopyridines (odds ratio, 0.84; 95% CI, 0.73 to 0.97). Although this meta-analysis possibly provided the highest level of evidence available prior to the publication of the head-to-head trials, we considered the finding that the fixed-dose combination of extended-release dipyridamole plus aspirin and clopidogrel are similar for the composite rate of vascular events (13.1% compared with 13.1%; hazard ratio, 0.99; 95% CI, 0.93 to 1.07), based on direct comparison in the PRoFESS trial, to be a more valid estimate of comparative treatment effectiveness.[42] There are a number of reasons why the effect estimates varied between the indirect network meta-analysis and the head-to-head PRoFESS trial. First, empirical evidence on the validity of indirect meta-analysis is still limited in general. Second, in this network meta-analysis, there was at least some potential for biasing of the treatment effects due to the authors' assumption of a class effect for thienopyridines (combined data from trials of clopidogrel compared to aspirin[24] and ticlopidine compared to aspirin)[45, 46] and the combining of data from trials of immediate-release and extended-release formulations of dipyridamole.

Comparisons to aspirin

Indirect evidence from aspirin-controlled trials of newer antiplatelet agents was consistent with direct evidence from head-to-head trials in suggesting no significant differences in effectiveness between extended-release dipyridamole plus aspirin and clopidogrel or between clopidogrel and ticlopidine. The fixed-dose combination of extended-release dipyridamole plus aspirin was the only included newer antiplatelet agent with evidence of a *statistically* significant advantage over aspirin alone in significantly reducing risk of recurrent stroke. But, compared to aspirin, extended-release dipyridamole plus aspirin, clopidogrel, and ticlopidine, respectively, all had similar relative risks of stroke reduction (range of relative risks, 0.84 to 0.94) and there was substantial overlap in the 95% confidence intervals around their relative risks (see Table 3). A possible explanation for lack of statistically significant results in the aspirin-controlled trials of clopidogrel and ticlopidine, respectively, may be their smaller sample sizes and more limited power.

Extended-release dipyridamole plus aspirin

The effect of the combination of extended-release dipyridamole plus aspirin has been compared to aspirin alone in 2 published[47, 48] randomized controlled trials and 1 unpublished[49] randomized controlled trial. Combined data from these trials distinguishes the combination of extended-release dipyridamole plus aspirin as being the only included newer antiplatelet agent with evidence of a significant advantage over aspirin alone in significantly reducing risk of any of the 3 major effectiveness outcomes listed in Table 3.

The 2 published trials included the Second European Stroke Prevention Study (ESPS-2)[47] and the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT).[48] The ESPS-2 consisted of 4 treatment arms: (1) extended-release dipyridamole 200 mg; (2) extended-release dipyridamole 200 mg and immediate-release aspirin 25 mg (extended-release dipyridamole/aspirin); (3) immediate-release aspirin 25 mg; and (4) placebo. ESPS-2 analyzed 6602 patients with a transient ischemic attack or completed ischemic stroke within the preceding 3 months. Patients were followed on treatment for 2 years. The ESPS-2 had 2 primary efficacy endpoints: stroke (fatal or nonfatal) and death from all causes. Among the co-primary endpoints, the combination of extended-release dipyridamole plus aspirin significantly reduced the risk of fatal and nonfatal stroke compared with very low-dose aspirin (9.5% compared with 12.5%;

relative risk, 0.76; 95% CI, 0.64 to 0.93; *P*=0.006), but the 2 groups were similar for the outcomes of stroke and/or death (17.3% compared with 20.0%; relative risk, 0.87; 95% CI, 0.74 to 1.0; *P*=0.056) and all-cause mortality (11.2% compared with 11.0%; relative risk, 1.02; 95% CI, 0.84 to 1.23; *P*=0.942).

ESPRIT was a randomized, controlled, nonblinded international study evaluating patients taking aspirin (median dose 75 mg; range, 30-325 mg) with (n=1363) or without (n=1376) extended-release dipyridamole within 6 months of a transient ischemic attack or minor stroke of presumed arterial origin. Follow-up time was for a mean of 3.5 years. Two-thirds of the patients were randomized 1-6 months after their event. The majority of the patients (83%) were administered extended-release dipyridamole as a separate component along with aspirin; 8% of the patients were on the combined aspirin/extended-release dipyridamole dosage form. Twenty-four patients from 1 hospital were excluded from all analyses because of incomplete data although this would not be expected to affect the overall outcome as the randomization process was stratified at the hospital level. For the primary outcome of first occurrence of the composite death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication, the combination of extended-release dipyridamole plus aspirin was significantly more effective in preventing events than aspirin alone (12.7% compared with 15.7%; relative risk, 0.81; 95% CI, 0.67 to 0.97).

The Japanese Aggrenox Stroke Prevention compared with Aspirin Program (JASAP) was a randomized, double-blind study designed to test noninferiority of the fixed-dose combination of extended-release dipyridamole 200 mg plus aspirin 25 mg taken twice daily over aspirin 81 mg taken once daily when given for 1 year. Although JASAP was completed in March of 2009, its results have not yet been published and are only available from ClinicalTrials.gov[50] and in the form of a tabulated trial report available on the manufacturer's website.[49] JASAP enrolled 1294 patients who had a noncardioembolic cerebral infarction with an onset in the previous week to 6 months. Although similar rates of the primary outcome of first recurrent cerebral infarction were found for the fixed-dose combination of extended-release dipyridamole plus aspirin compared with aspirin (6.9% compared with 5.0%; hazard ratio, 1.47; 95% CI, 0.93 to 2.31), unlike ESPS-2 and ESPRIT, JASAP demonstrated a trend toward increased risk with the fixed-dose combination of extended-release dipyridamole plus aspirin. In addition, the trial failed to demonstrate noninferiority of the fixed-dose combination of extended-release dipyridamole plus aspirin because the upper limit of the confidence interval (2.31) substantially exceeded the prespecified noninferiority margin of 1.37. Compared with the ESPS-2 and ESPRIT trials, the JASAP trial had a shorter follow-up duration (1.3 years vs. 2 and 3.5 years) and a higher prevalence of diabetes (40% vs. 15% and 19%) and hypertension (88% vs. 61% and 59%, respectively). However, none of these differences fully explained the heterogeneity between the JASAP and the ESPS-2 and ESPRIT trials.

Considering the inconsistency in relative risks across the JASAP, ESPS-2, and ESPRIT trials, there was moderate-strength evidence that the combination of extended-release dipyridamole is significantly more effective than aspirin alone in preventing recurrent stroke (Table 3).[47-49] For rates of all-cause mortality and cardiovascular mortality, however, our pooled analysis of data from these studies found moderate-strength evidence of no significant difference between the combination of extended-release dipyridamole plus aspirin and aspirin alone.

Table 3. Pooled relative risks of major outcomes for the comparison of each newer antiplatelet agent with aspirin alone following stroke or transient ischemic attack

Newer antiplatelet agent	All-cause mortality	Cardiovascular mortality	Stroke
Fixed-dose combination of extended-release dipyridamole plus aspirin	RR, 0.96 (0.83 to 1.13)	RR, 0.74 (0.51 to 1.08)	RR, 0.84 (0.73 to 0.98)
Clopidogrel	Not reported	RR, 0.99 (0.75 to 1.29)	RR, 0.92 (0.79 to 1.07)
Ticlopidine	RR, 0.94 (0.79 to 1.12)	RR, 1.16 (0.89 to 1.52)	RR, 0.94 (0.81 to 1.10)

Abbreviations: RR, relative risk.

Clopidogrel

The CAPRIE trial was designed to compare clopidogrel 75 mg once daily and aspirin 325 mg once daily in patients with ischemic stroke, myocardial infarction, or symptomatic atherosclerotic peripheral arterial disease.[24] Mean follow-up duration was 1.91 years. Although the CAPRIE trial randomized a total of 16 185 patients overall, here we are focusing only on results from the subgroup of 6451 patients with a history of ischemic stroke (mean age of 64.6 years, 63.5% male, 91% white). The subgroup analyses did not include the outcome of all-cause mortality, but provided moderate-strength evidence that clopidogrel and aspirin have similar effects in preventing cardiovascular mortality (fatal stroke, fatal myocardial infarction, other vascular death) and fatal and nonfatal stroke (Table 3 above).

Clopidogrel plus aspirin

When started early, within 24 hours of minor stroke symptom onset, treatment with clopidogrel 75 mg plus aspirin 81 mg (N=99) was compared to aspirin 81 mg alone (N=95) over 90 days in the fair-quality Fast Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence (FASTER) trial.[51] The FASTER trial also evaluated the potential role of simvastatin in stroke prevention when taken in combination with aspirin alone or with aspirin plus clopidogrel. However, as statin co-therapy is outside of the scope of this review, we did not discuss the effectiveness results of the simvastatin treatment arms here. On the primary outcome of any stroke (ischemic or hemorrhagic), although there was an absolute reduction of 4.4% for the combination of clopidogrel plus aspirin over aspirin use alone, the risk ratio analysis did not find this difference to be statistically significant (5.1% compared with 9.5%; risk ratio, 0.5; 95% CI, 0.2 to 1.5). However, as the FASTER trial was stopped early due to slow recruitment and did not meet its enrollment goal of 500 patients, it may not have had adequate statistical power to detect a significant difference. Rates of all-cause mortality and cardiovascular mortality were not reported.

Ticlopidine

Ticlopidine was compared to aspirin in 2 randomized controlled trials of patients with a recent stroke or transient ischemic attack.[45, 46] The first was the Ticlopidine Aspirin Stroke Study (TASS), which was a North American randomized, double-blind study comparing the effect of ticlopidine 250 mg twice daily to aspirin 650 mg twice daily in 3069 patients with recent transient or mild persistent focal cerebral or retinal ischemia. Mean follow-up was 40 months.[46]

In TASS,[46] there was no significant difference between ticlopidine and aspirin 650 mg in risk of death from any cause or the risk of nonfatal stroke (primary endpoint) (20% compared with 22.7%; relative risk, 0.88; 95% CI, 0.77 to 1.01; *P*=0.048). The cumulative event-rate curves for the incidence of stroke (nonfatal or fatal) was statistically significant between ticlopidine and aspirin at 5 years (11.2% compared with 13.8%; relative risk, 0.84; 95% CI, 0.69 to 1.01). However, the 95% confidence interval barely crossed 1, which raised the possibility that the 2 medications may be similar for this endpoint.

The second study was the African American Antiplatelet Stroke Prevention Study (AAASPS), which was a randomized, double-blind multicenter study comparing ticlopidine 250 mg twice daily and aspirin 325 mg twice daily for 2 years in 1809 African-American patients with a noncardioembolic ischemic stroke with onset of 7 days to 90 days prior to enrollment.[45] Ticlopidine and aspirin had similar effects on the primary composite outcome of recurrent stroke, myocardial infarction, or vascular death (14.7% compared with 12.3%; hazard ratio, 1.22; 95% CI, 0.94 to 1.57). Ticlopidine and aspirin also had similar effects on the secondary outcome of any recurrent fatal or nonfatal stroke (11.9% compared with 9.5%; hazard ratio, 1.28; 95% CI, 0.96 to 1.72).

Together, these trials provide moderate-strength evidence that ticlopidine and aspirin have similar effects on all-cause mortality, cardiovascular mortality, and fatal and nonfatal stroke (Table 3 above).

Peripheral Vascular Disease

We found no head-to-head trials that directly compared newer antiplatelet agents in patients with peripheral vascular disease. As indirect evidence, we included the peripheral arterial disease subgroup from the CAPRIE trial, which evaluated the comparison of clopidogrel and aspirin.[24] We also included the Clopidogrel and Acetylsalicylic acid in bypass Surgery for Peripheral Arterial disease (CASPAR) trial, which compared dual therapy with clopidogrel plus aspirin with aspirin alone.[52]

Clopidogrel compared with aspirin

The CAPRIE trial compared clopidogrel 75 mg to aspirin 325 mg daily over a mean follow-up duration of 1.91 years.[24] Data from the subgroup of 11 592 patients with peripheral arterial disease were provided for each of the individual events that comprised the combined primary outcome of ischemic stroke, myocardial infarction, and vascular death. For our analysis of cardiovascular death, we combined the number of events of fatal stroke, fatal myocardial infarction, and other vascular death and found no significant difference between clopidogrel and aspirin (1.6% compared with 2.1%; relative risk, 0.78; 95% CI, 0.60 to 1.01). Data from the peripheral arterial disease subgroup were not available for the outcomes of all-cause mortality or revascularization. On the primary composite outcome, compared to aspirin, there was a significant relative risk reduction with clopidogrel (23.8%; 95% CI, 8.9 to 36.2; 3.71% compared with 4.86%; *P*=0.0028).

Clopidogrel plus aspirin compared with aspirin alone

We included 2 randomized controlled trials for comparison of clopidogrel plus aspirin to aspirin alone in patients with peripheral vascular disease.[52, 53] Neither trial found significant benefits

with clopidogrel plus aspirin for all-cause mortality, cardiovascular mortality, or revascularization.

The first study was a post-hoc analysis of the subset of 3096 patients with peripheral arterial disease from the CHARISMA trial.[53] In the subset with peripheral arterial disease, sex was still predominantly male (70%), but the mean age of 66 years was slightly higher than in the overall CHARISMA population. Compared to aspirin alone, therapy with clopidogrel plus aspirin did not significantly reduce risk of death from any cause (6.7% compared with 7.5%; hazard ratio, 0.89; 95% CI, 0.68 to 1.16) or death from cardiovascular causes (4.2% compared with 4.6%; hazard ratio, 0.92; 95% CI, 0.65 to 1.28). However, due to the inherent limitations of post-hoc analyses, these results should be interpreted with caution until confirmed in an appropriately designed prospective trial.

The fair-quality CASPAR trial evaluated clopidogrel 75 mg plus aspirin (range, 75 mg to 100 mg) as compared to aspirin alone (range, 75 mg to 100 mg) for 364 days (median) in 851 patients undergoing unilateral, below-knee bypass graft for atherosclerotic peripheral arterial disease.[52] Sex was predominantly male (76%) and mean age was 66 years. Type of graft used was venous in 70% of patients and prosthetic in the other 30%. The primary combined endpoint was defined as the first occurrence of index graft occlusion, a surgical or endovascular revascularization procedure on the index bypass graft or para-anastomotic region, an amputation above the ankle of the index limb, or death. In the overall study population, compared with aspirin alone, dual therapy with clopidogrel plus aspirin did not significantly reduce risk of any of the secondary endpoints of all-cause mortality (5.6% compared with 4.0%; hazard ratio, 1.44; 95% CI, 0.77 to 2.68), cardiovascular mortality (incidence not reported; hazard ratio, 1.49; 95% CI, 0.73 to 3.01), or revascularization (incidence not reported; hazard ratio, 0.89; 95% CI, 0.65 to 1.23). Nor did dual therapy with clopidogrel plus aspirin significantly reduce the combined primary endpoint in the overall study population (35% compared with 35%; hazard ratio, 0.98; 95% CI, 0.78 to 1.23).

However, for the primary endpoint, a significant interaction was detected between treatment effect and type of graft used. Although there was no significant difference between dual therapy with clopidogrel and aspirin as compared to aspirin alone in the subgroup of patients with venous grafts (34% compared with 28%; hazard ratio, 1.25; 95% CI, 0.94 to 1.67), a significant benefit with clopidogrel plus aspirin was found in the group with prosthetic grafts (37% compared with 53%; hazard ratio, 0.65; 95% CI, 0.45 to 0.95). The benefit of clopidogrel plus aspirin in the prosthetic graft subgroup appeared to be primarily due to significant reductions in frequency of graft occlusions (32% compared with 47%; hazard ratio, 0.63; 95% CI, 0.42 to 0.93) and amputations (9% compared with 19%; hazard ratio, 0.48; 95% CI, 0.24 to 0.96), whereas no such interaction was found for the outcome of all-cause mortality. Results of subgroup analyses were not reported for the outcomes of cardiovascular mortality or revascularization.

Key Question 2. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in harms?

Summary of Findings

Direct evidence

- We found no direct evidence of the comparative harms of different newer antiplatelet agents in patients with acute coronary syndrome managed medically or with peripheral vascular disease.

Acute coronary syndrome managed with coronary revascularization via stenting or bypass grafting

- TRITON-TIMI 38, a good-quality randomized controlled trial that evaluated prasugrel compared with clopidogrel provided moderate-strength evidence of increased risk of major bleeding with prasugrel and no difference in withdrawal due to adverse events at 15 months.
- One good-quality randomized controlled trial (CLASSICS) that compared ticlopidine to clopidogrel provided moderate-strength evidence of no difference in risk of major bleeding at 28 days. It also provided low-strength evidence of increased withdrawals due to adverse events with ticlopidine. No significant differences between ticlopidine and clopidogrel were found after 30 days in a fair-quality observational study or after 6 months in a fair-quality randomized controlled trial.

Stroke or transient ischemic attack

- The PRoFESS trial provided moderate-strength evidence of a higher risk of major bleeding with the fixed-dose combination of extended-release dipyridamole plus aspirin than clopidogrel and high-strength evidence of increased withdrawals due to adverse events with the fixed-dose combination of extended-release dipyridamole plus aspirin.
- Two trials provided moderate-strength evidence that, compared with ticlopidine, clopidogrel had a lower risk of neutropenia (1% compared with 3%; relative risk, 0.32; 95% CI, 0.15 to 0.65) and overall withdrawals due to adverse events (14% compared with 20%; relative risk, 0.71; 95% CI, 0.58 to 0.87). Rate of major bleeding was not significant in the clopidogrel and ticlopidine groups (1.5% compared with 1.0%; relative risk, 1.53; 95% CI, 0.68 to 3.45).

Indirect evidence

Acute coronary syndrome managed medically

- One good-quality randomized controlled trial (CURE) provided moderate strength evidence of increased risk of major bleeding at 12 months with clopidogrel plus aspirin compared with aspirin alone.

Stroke or transient ischemic attack

- Two published trials (ESPS-2, ESPRIT) and 1 unpublished trial (JASAP) consistently found no significant difference between extended-release dipyridamole plus aspirin and aspirin alone in frequency of major bleeding. However, withdrawal due to adverse events with the combination of extended-release dipyridamole plus aspirin was significantly greater in 2 of 3 trials.
- There was no evidence available to evaluate the comparative harms between clopidogrel and aspirin in patients following a transient ischemic attack or a stroke.
- When added to aspirin within 24 hours of symptom onset, there was no significant increase in risk of severe extracranial bleeding with clopidogrel compared with taking aspirin alone. Overall, major bleeding and withdrawals due to adverse events were not reported.
- When compared with 1300 mg of aspirin daily over 40 months in primarily white patients, ticlopidine had a significantly lower rate of gastrointestinal bleeding but significantly higher rates of withdrawals due to adverse events and severe neutropenia. When compared to 650 mg of aspirin daily over 24 months in black patients, the differences with ticlopidine on those same harms were smaller and not significant.

Peripheral vascular disease

- Compared with aspirin alone, major bleeding risk was not significantly increased during dual therapy with clopidogrel plus aspirin. Incidence of withdrawals due to adverse events was not reported.

Detailed Assessment

Acute coronary syndrome

Direct evidence

In the CURE[21] trial, adding clopidogrel to aspirin provided benefit regardless of the aspirin dose but with a higher incidence of bleeding. For patients with acute coronary syndrome, a statistically significant higher incidence of major bleeding occurred in the clopidogrel and aspirin group compared with the placebo plus aspirin group (3.7% compared with 2.7%; relative risk, 1.38; 95% CI, 1.13 to 1.67; P=0.001, absolute risk reduction, 1%; number needed to treat, 100). A nonsignificant higher incidence of life-threatening bleeding occurred in the clopidogrel group (2.2% compared with 1.8%; relative risk, 1.21; 95% CI, 0.95 to 1.56; not significant). Minor bleeding episodes were twice as common with clopidogrel than with placebo. Though not powered to detect differences in bleeding rates by aspirin dose, a post-hoc analysis[22] from the CURE trial suggested that lower aspirin doses (75-100 mg) with clopidogrel have more favorable safety profiles in terms of bleeding rates compared to when clopidogrel was combined with higher doses of aspirin. In the CURE[21] trial, 21.1% of the patients in the clopidogrel plus aspirin group discontinued the study medication permanently, compared with 18.8% in the placebo plus aspirin group (P=0.001). The discontinuation rates due to adverse events were comparable between clopidogrel and placebo.

In the CHARISMA[23] trial the rates of severe bleeding among the symptomatic subgroup patients were 1.6% and 1.4% and were not significant. The rate for moderate bleeding in the symptomatic group was significant and was reported as 2.1% with clopidogrel compared with 1.3% in the placebo group (P<0.001). In CHARISMA[23] trial, treatment was permanently

discontinued by 20.4% of the patients in the clopidogrel group as compared with 18.2% in the placebo group ($P<0.001$). Reasons for permanently discontinuing therapy were not provided in the main publication. A total of 4.8% of the patients in the clopidogrel group and 4.9% in the placebo group discontinued treatment because of an adverse event ($P=0.67$).

In the CAPRIE[54] trial, the incidence of permanent discontinuation rates of the study drug due to adverse events was comparable between clopidogrel and aspirin (13%). The most common reason for adverse event-related early permanent discontinuations was a gastrointestinal event (3.21% for clopidogrel and 4.02% for aspirin).

Acute coronary syndrome managed with coronary revascularization via stenting or bypass grafting

Direct evidence

Prasugrel compared with clopidogrel

The 15-month TRITON-TIMI 38[25] trial reported noncoronary artery bypass graft surgery-related TIMI major bleeding for prasugrel (2.4%) compared with clopidogrel (1.8%) (relative risk, 1.32; 95% CI, 1.03 to 1.68, $P=0.03$; absolute risk reduction, 0.5%; number needed to treat, 167). Life-threatening bleeding was reported for prasugrel (1.4%) compared with clopidogrel (0.9%) (hazard ratio, 1.52; 95% CI, 1.08 to 2.13, $P=0.01$). Total withdrawals due to adverse events for prasugrel compared with clopidogrel were 7.2% compared with 6.4% (relative risk, 1.14; 95% CI, 1.00 to 1.29). Withdrawals related to hemorrhage were 2.5% for prasugrel compared with 1.4% for clopidogrel ($P<0.001$).

Clopidogrel compared with ticlopidine

In the 28-day CLASSICS[29] trial, clopidogrel was better tolerated than ticlopidine in the primary endpoint (major peripheral bleeding complications, neutropenia or thrombocytopenia, or early discontinuation of study drug as the result of a noncardiac adverse event during the study-drug treatment period) (4.6% compared with 9.1%; $P=0.005$). The most frequent reason for early discontinuation of study drug as the result of a noncardiac adverse event during the study-drug treatment period was skin disorders, primarily rash. The incidence for skin disorders occurred in 2.6% of the ticlopidine group and in 0.7% of the combined clopidogrel groups. One ticlopidine patient (0.3%) developed neutropenia (neutrophil $<0.1 \times 10^9$/L) 28 days after randomization. Four clopidogrel patients (0.6%) had mild and transient thrombocytopenia; 3 of them had received heparin concomitantly. The rates of major peripheral or bleeding complication were similar in all treatment groups: ticlopidine (1.2%) compared with clopidogrel 75 mg (1.2%) compared with clopidogrel 300 mg/75 mg (1.5%). The corresponding bleeding risk for ticlopidine compared with clopidogrel 75 mg was relative risk, 0.99 (95% CI, 0.27 to 3.57; not significant).

Di Pasquale, et al.[31] conducted a double-blind, randomized, single-center trial comparing ticlopidine 500 mg daily to clopidogrel 75 mg daily in 428 patients hospitalized with an admission diagnosis of first episode of acute coronary syndrome. It reported no difference in major bleeding between ticlopidine compared with clopidogrel (relative risk, 1; 95% CI, 0.178 to 5.63; not significant).

One fair-quality observational trial[55] that evaluated ticlopidine compared with clopidogrel provided low-strength evidence of no difference in risk of major bleeding at 30 days. The retrospective analysis included 311 Japanese patients who had stent implantation between

January 2007 and April 2009. The primary endpoint was major bleeding 30 days: clopidogrel (4.4%) compared with ticlopidine (3.9%) (odds ratio, 1.12; 95% CI, 0.31 to 4.14; *P*=0.94).

Indirect evidence

One fair-quality observational trial[56] that compared clopidogrel within 5 days of coronary artery bypass graft surgery (Group A) with clopidogrel more than 5 days after coronary artery bypass graft surgery (Group B) provided low-strength evidence of increased risk of major bleeding at 30 days. This was a retrospective cohort analysis performed of randomly selected acute coronary syndrome patients requiring coronary artery bypass graft surgery in 14 hospitals across the United States. Major bleeding occurred in 35% of Group A patients compared with 26% of Group B patients (*P*=0.049). Control for confounding using the propensity score method demonstrated an increased risk for major bleeding (odds ratio, 1.82; 95% CI, 1.11 to 3.01; *P*=0.02).

Stroke or transient ischemic attack

Direct evidence

Three head-to-head trials provided moderate-strength evidence that clopidogrel may have a somewhat better adverse effect profile than other newer antiplatelet agents, in that patients receiving clopidogrel had a lower rate of major bleeding than with the fixed-dose combination of extended-release dipyridamole plus aspirin[42] and had a lower rate of neutropenia than with ticlopidine.[41, 43] As described above, the good-quality PRoFESS trial compared 2.5 years of treatment (mean) with either the fixed-dose combination of aspirin 25 mg and extended-release dipyridamole 200 mg or clopidogrel 75 mg in 20 332 patients who had had an ischemic stroke within 90 days of study entry. In the PRoFESS trial, in patients receiving the fixed-dose combination of extended-release dipyridamole plus aspirin, there was a higher rate of major bleeding (4.1% compared with 3.6%; hazard ratio, 1.15; 95% CI, 1.00 to 1.32) as well as a higher rate of withdrawal due to adverse events (16.4% compared with 10.6%; relative risk, 1.54; 95% CI, 1.43 to 1.66).

Combined results from 2 fair-quality randomized controlled trials of 1869 Japanese patients with stroke found a lower rate of both neutropenia (1% compared with 3%; relative risk, 0.32; 95% CI, 0.15 to 0.65) and overall withdrawals due to adverse events (14% compared with 20%; relative risk, 0.71; 95% CI, 0.58 to 0.87) with clopidogrel 75 mg than with ticlopidine 200 mg.[41, 43] There was no significant difference between clopidogrel and ticlopidine in rate of major bleeding (1.5% compared with 1.0%; relative risk, 1.53; 95% CI, 0.68 to 3.45).

Indirect evidence

Extended-release dipyridamole plus aspirin compared with aspirin alone

The difference between extended-release dipyridamole plus aspirin and aspirin alone in frequency of major bleeding was not statistically significant in 2 published trials[47, 48] and 1 unpublished trial.[49] In the ESPS-2 trial (N=3299), over 2 years, severe or fatal bleeding occurred in 1.6% of patients during treatment with extended-release dipyridamole 200 mg plus immediate-release aspirin 25 mg and in 1.2% with aspirin 25 mg alone (relative risk, 1.35; 95% CI, 0.76 to 2.40).[47] In the ESPRIT trial (N=2739), frequency of major bleeding at 3.5 years was somewhat lower during treatment with extended-release dipyridamole 200 mg plus immediate-release aspirin 75 mg compared with aspirin 75 mg alone (2.9% compared with 3.9%; relative risk, 0.67; 95% CI, 0.44 to 1.01).[48] In the manufacturer's synopsis of results from the

unpublished JASAP trial (N=1294), the frequencies of major bleeding events at 1 year were described as comparable for extended-release dipyridamole 200 mg plus aspirin 25 mg and aspirin 81 mg alone, but the data was not reported.[49]

Compared with aspirin alone, risk of withdrawal due to adverse events was significantly increased with the combination of extended-release dipyridamole plus aspirin in 2[47, 48] of 3 trials.[47-49] Despite follow-up durations that ranged from 1 year (JASAP)[49] to 3.5 years (ESPRIT),[48] frequency of withdrawals due to adverse events with the combination of extended-release dipyridamole plus aspirin remained fairly consistent across trials (range, 16% to 19%). However, frequency of withdrawals due to adverse events in the aspirin-only control groups varied widely across trials (range, 3% to 16%), which could not be explained by population, dosage level (range, 50 mg to 81 mg), or follow-up duration. For example, based on the premise that withdrawals due to adverse events may naturally increase over longer periods of time, one might generally expect to see a lower frequency of withdrawals due to adverse events in shorter-term trials. However, among these trials, at 16%, frequency of withdrawals due to adverse events in the aspirin-only control group was highest in the shortest-term, unpublished trial (JASAP), and, at 3%, was lowest in the longest-term, ESPRIT trial. Therefore, because of this unexplained heterogeneity, we did not combine data from these trials to generate a pooled relative risk for the comparison of combination treatment with extended-release dipyridamole plus aspirin to aspirin alone. In the JASAP trial, compared to aspirin alone, withdrawal due to adverse events was only slightly higher for the combination of extended-release dipyridamole plus aspirin at 1 year (18% compared with 16%; relative risk, 1.10; 95% CI, 0.86 to 1.39).[49] Whereas after 2 years in the ESPS-2 trial, the relative risk of withdrawals due to adverse events with the combination of extended-release dipyridamole plus aspirin increased to 1.86 (95% CI, 1.53 to 2.25; 16% compared with 9%).[47] Finally, after 3.5 years in the ESPRIT trial, the relative risk of withdrawals due to adverse events with the combination of extended-release dipyridamole plus aspirin increased further to 7.35 (95% CI, 5.22 to 10.38; 19% compared with 3%).

As for other adverse events, compared with aspirin alone, frequency of headache was significantly greater with the combination of extended-release dipyridamole plus aspirin in the 2 trials that reported this outcome (40% compared with 32%, pooled relative risk, 1.26; 95% CI, 1.16 to 1.36).[47, 49]

Clopidogrel compared with aspirin

In the CAPRIE trial, although effectiveness outcomes were reported for the subgroup of 6451 patients with a history of ischemic stroke, harms outcomes were not reported separately for this subgroup. Therefore, there was no evidence available to evaluate the comparative harms between clopidogrel and aspirin in patients following a transient ischemic attack or a stroke.

Clopidogrel plus aspirin compared with aspirin alone

Reporting of harms was limited in the FASTER trial, which compared early treatment (within 24 hours) with clopidogrel 75 mg plus aspirin 81 mg (N=99) to aspirin 81 mg alone (N=95).[51] The FASTER trial also used a factorial design to randomize patients to clopidogrel or placebo and simvastatin or placebo. For effectiveness outcomes, separate data was available for the comparison of clopidogrel plus aspirin to aspirin alone in patients who were not taking simvastatin. However, for harms, data was only available for the comparison of clopidogrel to no clopidogrel in all patients, regardless of simvastatin use. However, the risk of confounding of bleeding outcomes based on simvastatin use was likely low as there is no known link between

simvastatin and bleeding risk. Although overall major bleeding and withdrawals due to adverse events were not reported, compared to no clopidogrel, clopidogrel use was not found to significantly increase risk of severe extracranial bleeding (0.5% compared with 0%; risk difference, 0.5%; 95% CI, –0.5 to 1.5).

A second observational study of 633 patients evaluated the risk of major bleeding with aspirin plus clopidogrel compared with aspirin alone when given early after stroke or transient ischemic attack.[57] However, its results will not be discussed here because it had significant differences in clinical characteristics between groups at baseline but conducted no statistical analysis to adjust for these potential confounders.

Ticlopidine compared with aspirin

Among 2 randomized controlled trials,[45, 46] differences in harms between ticlopidine and aspirin only reached statistical significance in the larger (N=3069), longer-term (40 months) TASS trial, which involved a higher dosage in the aspirin control group (1300 mg) and enrolled primarily white patients (80%).[46] In the TASS trial, when compared to 1300 mg of aspirin, there was a significantly lower risk of gastrointestinal bleeding with ticlopidine (0.5% compared with 1.4%; relative risk, 0.34; 95% CI, 0.14 to 0.79). However, withdrawals due to adverse events were significantly greater with ticlopidine (21% compared with 14%; relative risk, 1.23; 95% CI, 1.23 to 1.68), as was frequency of severe neutropenia, defined as absolute neurophil count less than 450/cubic millimeter (0.8% compared with 0%). In contrast, in the 2-year AAASPS trial of 1809 black patients, when compared to aspirin 650 mg, ticlopidine had similar rates of gastrointestinal bleeding (0.4% compared with 0.9%; relative risk, 0.50; 95% CI, 0.16 to 1.56), withdrawals due to adverse events (9% compared with 8%; relative risk, 1.15; 95% CI, 0.85 to 1.55), and any neutropenia (3.4% compared with 2.2%; relative risk, 1.56; 95% CI, 0.90 to 2.70).[45]

Peripheral vascular disease

Indirect evidence

Clopidogrel compared with aspirin

In the CAPRIE trial, data on harms were not reported separately for the subgroup of 11 592 patients with peripheral vascular disease.[24]

Clopidogrel plus aspirin compared with aspirin alone

Two trials were consistent in finding no significant increase in major bleeding with clopidogrel plus aspirin compared with aspirin alone.[52, 53] In the subset of 3096 patients from the CHARISMA trial, rate of severe bleeding was identical for clopidogrel plus aspirin and aspirin alone (1.7% compared with 1.7%; hazard ratio, 0.97; 95% CI, 0.56 to 1.66).[53] In the CASPAR trial (N=851), the 1-year (median) incidence of severe bleeding was close to doubled during dual therapy with clopidogrel 75 mg plus aspirin (range, 75 mg to 100 mg) as compared with aspirin alone (range, 75 mg to 100 mg), but the difference was not statistically significant (2.1% compared with 1.2%; relative risk, 1.78 ; 95% CI, 0.63 to 5.04).[52] Incidence of withdrawal due to adverse events was not reported.

Key Question 3. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in effectiveness and harms based on duration of therapy?

Summary of Findings

- We found no head-to-head trials that directly compared newer antiplatelet agents based on duration of therapy.
- Compared with 1 month of treatment with clopidogrel plus aspirin, there was moderate-strength evidence of a significant reduction in risk of revascularization with 6 months of treatment, with no significant increase in bleeding risk. The benefit appeared to decrease in a step-wise manner and lose statistical significance at 8 months (PCI-CURE, low strength) and 12 months (CREDO, moderate strength).

Detailed Assessment

Indirect evidence

Current percutaneous coronary intervention guidelines[5] recommend the duration of thienopyridine therapy for patients receiving a bare metal stent or drug eluting stent during percutaneous coronary intervention for acute coronary syndrome be at least 12 months. If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered. Early discontinuation of thienopyridine therapy has been identified as a risk factor for late stent thrombosis in patients with drug eluting stent but the optimal therapy and comparative risk-benefit of bare metal stent compared with drug eluting stent remains uncertain.[58, 59] This controversy is beyond the scope of this report.

We included 3 fair-quality trials[60-62] comparing 6 months of dual therapy (clopidogrel and aspirin) to 1 month of dual therapy, the PCI-CURE trial[63] comparing an average of 8 months of dual therapy to 1 month, and the CREDO trial[64] comparing 12 months of dual therapy to 1 month. Among the 3 trials that evaluated 6 months of dual therapy, the first evaluated clopidogrel 75 mg plus aspirin 100 mg in 278 Turkish patients with successful stent implantation.[62] The second trial evaluated clopidogrel 75 mg plus aspirin 300 mg in 78 Turkish patients with typical stable angina pectoris or documented myocardial ischemia, and with only 1 angiographic lesion in 1 native coronary artery undergoing successful stent implantation.[60] The Randomized Argentine Clopidogrel Stent (RACS) trial was a prospective, randomized, nonblinded study of 1004 patients undergoing percutaneous coronary intervention who were randomized after successful bare metal stent placement to 30 compared with 180 days of clopidogrel 75 mg plus aspirin 75 to 325 mg.[61] The PCI-CURE trial included 2658 patients with non-ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention.[63] Following percutaneous coronary intervention, after 2 to 4 weeks of open-label clopidogrel or ticlopidine, patients were randomized to a mean of 8 months of continuing treatment with clopidogrel plus aspirin 75 to 325 mg or to placebo. Similarly, in the CREDO trial, after percutaneous coronary intervention, 2116 patients received open-label clopidogrel 75 mg for 28

days and then were randomly assigned to double blind treatment with continuation of clopidogrel 75 mg plus aspirin 325 mg for 12 months or to aspirin 325 mg alone.[64]

When we used a fixed-effects model to pool data from the 3 trials that compared 6 months of treatment with clopidogrel plus aspirin to 1 month of treatment for the outcomes of all-cause mortality, cardiovascular mortality, revascularization, and bleeding, a significant benefit with the longer-term treatment was only found for the outcome of revascularization (relative risk, 0.65; 95% CI, 0.15 to 1.65) and there was no significant increase in risk of bleeding (Table 4). No other pooled outcome reached statistical significance. Only the RACS trial reported withdrawals due to adverse events but it was a nonsignificant and imprecise finding (relative risk, 2.20; 95% CI, 0.81 to 6.04).[61]

In contrast, when we considered results for revascularization from the PCI-CURE and CREDO trials, we observed that the potential benefit of a reduced risk of revascularization became only probable at 8 months was unlikely at 12 months (Table 4, Figure 2). There was also a trend toward increased bleeding risk over time when results from the PCI-CURE and CREDO trials were considered (Table 4, Figure 3).

Table 4. Detailed outcome data from pooled analysis of dual antiplatelet therapy length postpercutaneous coronary intervention

Therapy length	N	All-cause mortality (95% confidence interval)	Cardiovascular mortality (95% confidence interval)	Revascularization (95% confidence interval)	Bleeding (95% confidence interval)
6 months	1199[64,65]	0.86 (0.4 to 1.84)			
	999[63,64]		0.50 (0.15 to 1.65)		
	1277[63,64,65]			0.65 (0.43 to 0.97)	1.01 (0.44 to 2.30)
8 months PCI-CURE[15]	2658	NR	1.07 (0.65 to 1.75)	0.82 (0.68 to 1.00)	1.12 (0.70 to 1.78)
12 months CREDO[16]	2116	0.7 (0.58 to 1.00)	NR	1.01 (0.86 to 1.20)	1.32 (0.98 to 1.78)

Akbulut 2004[60] n=78; Pekdemir 2003[62] n=278; Bernardi 2007[61] n=921.

Figure 2. Revascularization risk at 6 months, 8 months, and 12 months

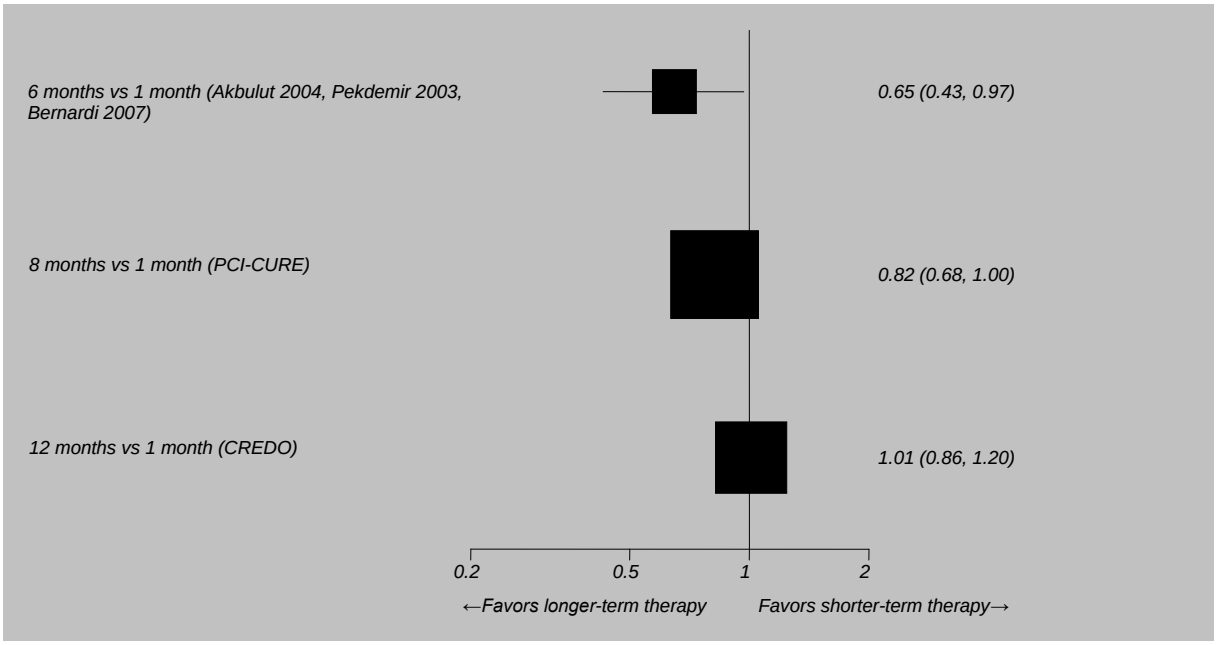
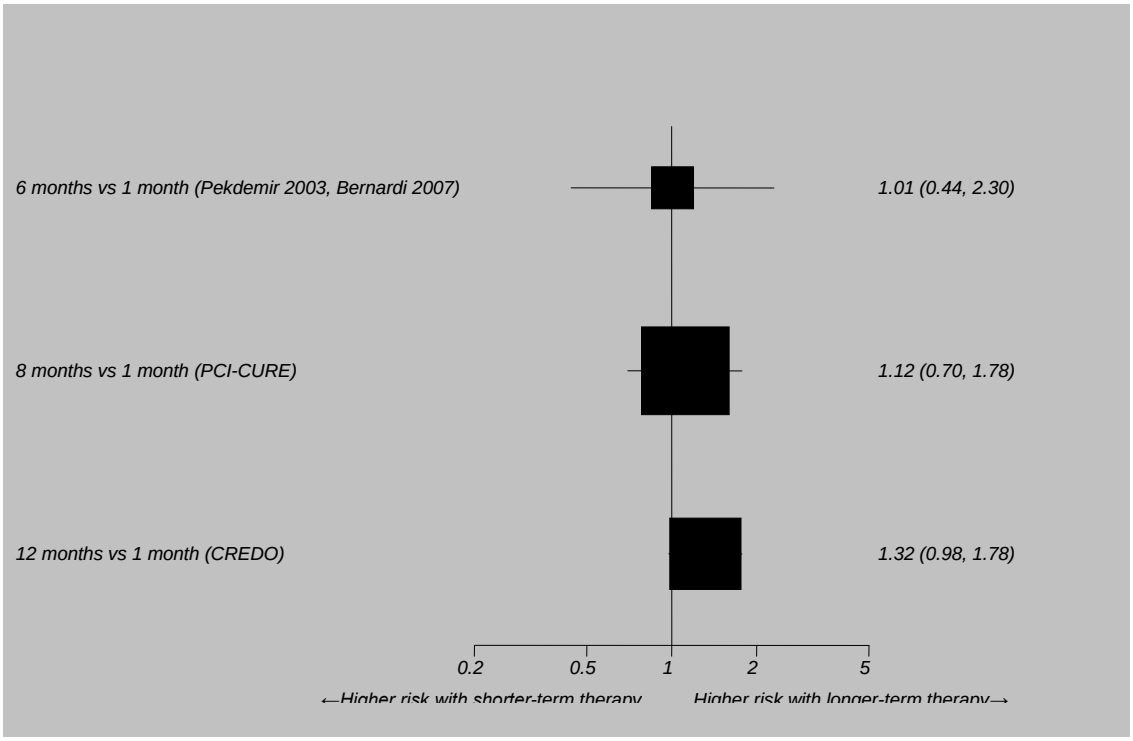


Figure 3. Major bleeding risk at 6 months, 8 months, and 12 months



The CREDO[64] trial also demonstrated a long-term (1-year) reduction in the primary composite outcome of death, myocardial infarction, or stroke over short-term (1-month) therapy

in patients undergoing percutaneous coronary intervention with clopidogrel and aspirin (8.5% compared with 11.5%; relative risk, 0.73; 95% CI, 0.57 to 0.95; *P*=0.021, number needed to treat, 33). The component outcomes of all-cause mortality and revascularization did not reach statistical significance because the study was not powered to detect a difference. All-cause mortality relative risk of clopidogrel long-term compared with short-term was 0.86 (95% CI, 0.04 to 1.84; absolute risk reduction, 0.6%). The revascularization relative risk of clopidogrel long-term compared with short-term was 1.01 (95% CI, 0.86 to 1.20). In contrast, a nonsignificant increase in the risk of major bleeding at 1 year occurred (relative risk, 1.32; 95% CI, 0.98 to 1.78; absolute risk reduction, 2.1%, number needed to harm, 48). This study was limited by > 40% of the patients not completing the study drug treatment for 1 year with either the active medication or placebo. Reasons why patients (n=94) discontinued study medications prior to percutaneous coronary intervention were not provided. Following the percutaneous coronary intervention procedure, approximately 46% of the patients in both groups permanently discontinued treatment. The occurrence of an adverse event was the reason for permanently discontinuing the study medication in 34.5% clopidogrel users and in 28.3% of those receiving placebo (*P*=0.054). As a secondary objective, CREDO[64] evaluated a pretreatment loading dose of clopidogrel 300 mg ≥ 6 hours prior to percutaneous coronary intervention which reduced the relative risk reduction of 38.6% for the combined primary endpoint at 28 days, but that result was of borderline statistical significance (*P*=0.051).

The PCI-CURE[63] trial was a predefined sub-study of the CURE population that evaluated the outcomes of patients undergoing percutaneous coronary intervention. This study examined the role of clopidogrel prior to (mean of 6 days before intervention) and after percutaneous coronary intervention. PCI-CURE[63] trial found that with long-term (8 months on average) administration of clopidogrel and aspirin after percutaneous coronary intervention, the rates of the primary composite outcome of cardiovascular death, myocardial infarction, or any revascularization were lower (relative risk, 0.75; 95% CI, 0.56 to 1.00; *P*=0.047; absolute risk reduction, 3.4%, number needed to treat, 29). The component outcomes of cardiovascular death or revascularization did not reach statistical significance because the study was not powered to do so. There was not a difference in cardiovascular deaths with clopidogrel at ~8 months of treatment compared with 1 month of treatment (relative risk, 1.07; 95% CI, 0.65 to 1.75). There was a trend towards lower risk of revascularization for clopidogrel patients (relative risk, 0.82; 95% CI, 0.68 to 1.00). At the end of follow-up in the PCI-CURE[63] trial (average 8 months), the only statistical significant difference in bleeding for clopidogrel compared with aspirin was minor bleeding episodes. Major bleeding risk was relative risk, 1.12 (95% CI, 0.70 to 1.78).

Two fair-quality observational studies[65, 66] evaluated bleeding risk associated with long-term clopidogrel use postpercutaneous coronary intervention. Banerjee 2008 was a retrospective cohort study that evaluated the outcomes of 530 consecutive patients who underwent percutaneous coronary intervention from January 2004 to July 2006, were free of cardiovascular events for 6 months after percutaneous coronary intervention, and had follow-up available for more than 12 months.[65] The outcomes of patients who received clopidogrel for more than 1 year were compared with those of patients who received it for less than 1 year. The incidence of major bleeding for greater than 1 year compared with less than 1 year was 5% compared with 3.2% (relative risk, 1.56; *P*=0.24). Peterson 2010 was a retrospective cohort study of 9256 patients receiving drug-eluting stents between January 2003 and August 2006.[66] Patients were classified according to tertiles of clopidogrel use during the 12 months after stent implantation. Inverse probability weighting was used to account for differential selection into levels of

clopidogrel use and logistic regression to estimate propensity scores for levels of clopidogrel use. High use was defined as daily use. Higher clopidogrel use 12 months after drug-eluting stent implantation was associated with a greater risk of subsequent bleeding events.

One fair-quality observational trial looked at antiplatelet medication use by prospectively evaluating 591 off-pump coronary artery bypass graft surgery patients.[67] Clopidogrel was administered for 30 days in 186 patients and 139 received long-term clopidogrel (mean 33.6 $\pm$ 12.0 months) in addition to aspirin. Follow-up was 37.7 $\pm$ 13.4 months. Symptom recurrence (angina and congestive heart failure), adverse cardiac events (myocardial infarction, coronary re-intervention, and sudden cardiac death), and overall mortality were prospectively recorded. However, Drug Effectiveness Review Project methods restrict use of observational studies to evaluate harms. There were 17 bleeding complications (4 major and 13 minor) in 15 patients during the follow-up period. Of the 15 patients, 6 were on clopidogrel in addition to aspirin (1.8%) while the remaining 9 were on aspirin only (3.3%) at the time of bleeding (P=0.8).

Key Question 4. Are there subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one antiplatelet agent is more effective or associated with fewer harms?

Summary of Findings

Age

- There was no significant interaction between age and the relative effects of prasugrel and clopidogrel on the primary composite endpoint (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) but a post-hoc analysis suggested no net benefit from prasugrel for patients 75 years of age or older.
- The fixed-dose combination of extended-release dipyridamole plus aspirin did not meet predefined criteria for noninferiority compared with clopidogrel for the primary outcome of recurrent stroke across all patients in the PRoFESS trial, and the relative difference between antiplatelet agents was consistent across subgroups of patients based on age.

Race

- The fixed-dose combination of extended-release dipyridamole plus aspirin did not meet predefined criteria for noninferiority compared with clopidogrel for the primary outcome of recurrent stroke across all patients in the PRoFESS trial, and the relative difference between antiplatelet agents was consistent across subgroups of patients based on race.

Gender

- No significant interaction was found between sex and the relative effect of prasugrel compared with clopidogrel in the TRITON-TIMI 38 trial.
- The fixed-dose combination of extended-release dipyridamole plus aspirin did not meet predefined criteria for noninferiority compared with clopidogrel for the primary outcome of recurrent stroke across all patients in the PRoFESS trial, and the relative difference between antiplatelet agents was consistent across subgroups of patients based on gender.

Comorbidities

- A subgroup analysis of the TRITON-TIMI 38 trial found that, compared with clopidogrel, there was a significantly greater reduction in risk of the composite primary endpoint with prasugrel in patients with and without diabetes.
- A post-hoc analysis of TRITON-TIMI 38 suggested that patients who had a previous stroke or transient ischemic attack had net harm from prasugrel.
- A post-hoc analysis of TRITON-TIMI 38 suggested that patients weighing less than 60 kg had no net benefit from prasugrel.
- A subgroup analysis of the PRoFESS trial found that the relative difference between the fixed-dose combination of extended-release dipyridamole plus aspirin and clopidogrel for the primary outcome of recurrent stroke was consistent both in patients with and without diabetes or obesity.

Other medications

- Evidence was insufficient to draw conclusions about the benefit-risk ratio of using a proton pump inhibitor in patients taking clopidogrel. We found no randomized controlled trials specifically designed to assess whether concomitant use of a proton pump inhibitor increased the risk of cardiovascular events in patients taking clopidogrel. Indirect evidence indicated that although use of a proton pump inhibitor significantly reduced risk of hospitalization for gastroduodenal bleeding in a broadly-defined average-risk patient population who were taking clopidogrel (without aspirin), there was no significant reduction in risk of rehospitalization for major gastrointestinal complications in patients at high risk for gastrointestinal bleeding.
- We found no evidence of the potential gastrointestinal benefits or cardiovascular harms of taking a proton pump inhibitor with any other newer antiplatelet agent.
- Compared to aspirin alone, the increased risk of nonfatal and fatal bleeding with clopidogrel plus a Vitamin K antagonist was almost 3 times higher than with Vitamin K antagonist alone, and was similar to the risk with triple therapy (aspirin, clopidogrel, Vitamin K antagonist).

Genotype

- In clopidogrel-treated patients with coronary stent placement, there was no significant difference between carriers of the CYP2C19*17 allele and noncarriers in risk of major bleeding at 30 days.
- In a genetic substudy of the TRITON-TIMI 38 involving patients with acute coronary syndromes undergoing percutaneous coronary intervention, there was no significant difference between patients with the *ABCB1* 3435 TT genotype and those without (*ABCB1* 3435 CC or CT genotypes) in the combined rate of TIMI major or minor bleeding at 12 months.
- As we found no eligible randomized controlled trials specifically designed to evaluate the potential effects of genotypes on the risk of cardiovascular events in patients taking newer antiplatelet agents, we could not draw any conclusions on this topic.

Detailed Assessment

Demographics

Age

Direct evidence

In the TRITON-TIMI 38 trial of patients with acute coronary syndromes scheduled for a percutaneous coronary intervention, Kaplan-Meier estimated hazard ratios for selected subgroups of patients for the primary composite endpoint (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) were reported. No statistically significant interactions were identified. The overall hazard ratio for prasugrel compared with clopidogrel was 0.81. The reduction in risk was significantly greater for prasugrel in patients younger than 65 years old (hazard ratio, 0.76), but was less impressive and nonsignificant in patients 65-74 years (hazard ratio, 0.87) and patients at least 74 years old (hazard ratio, 0.94). The authors performed a series of post-hoc exploratory analyses to identify subgroups of patients who did not have a favorable net clinical benefit. This was defined as the rate of death from any cause, nonfatal myocardial infarction, nonfatal stroke, or noncoronary artery bypass graft-related nonfatal major bleeding. Patients 75 years of age or older had no net benefit from prasugrel (hazard ratio, 0.99; 95% CI, 0.81 to 1.21; *P*=0.92).

In 20 332 patients with recent ischemic stroke who participated in the good-quality PRoFESS trial,[42] the predefined criteria for noninferiority of the fixed-dose combination of extended-release dipyridamole plus aspirin compared with clopidogrel were not met for the primary outcome of recurrent stroke. The relative difference between extended-release dipyridamole plus aspirin and clopidogrel was consistent in subgroups of patients who were less than 65 years of age (7.7% for both groups), 65 to 75 years of age (9.5% compared with 9.3%), or 75 years of age or greater (11.1% compared with 10.6%). Results of the hazard ratio analysis were displayed in graphical form, but the actual hazard ratios and 95% confidence intervals were not reported.

Indirect evidence

In a subset analysis of CURE,[21] compared with placebo plus aspirin, clopidogrel plus aspirin showed benefit in the rates of the first primary outcome in patients more than 65 years old (13.3% compared with 15.3%), as it did in those 65 years old or younger (5.4% compared with 7.6%).

A separate analysis of the ESPS-2[68] trial was performed for 3 age categories: less than 65 years (n=2565; 39%), 65 to 74 years (n=2240; 34%), and 75 years or older (n=1797; 27%). In that analysis, extended-release dipyridamole/aspirin was superior to either agent used alone in the secondary prevention of ischemic stroke, irrespective of age. While these data refer to adults, the product contains aspirin and thus should be avoided in children and teenagers with viral infection due to the risk of Reye's syndrome.

In a subgroup analysis of the ESPRIT[48] trial, compared to aspirin alone, there was a trend toward increased benefit with the fixed-dose combination of extended-release dipyridamole plus aspirin on the primary composite outcome regardless of age (65 years old and younger compared with over 65 years old).

One case-control study[69] evaluated bleeding among elderly nursing home residents who were stroke survivors from 1992 to 1997. These patients, on various antiplatelet and

anticoagulant agents for secondary stroke prevention, were predominantly female (68.8%) and of white, non-Hispanic descent (80.8%). The study was designated as poor quality due to its methodological limitations, but it suggested that patients aged 75 to 84 years and those who were more than 85 years old were more likely to have a bleed than were younger patients. After adjusting for various factors (including age, gender, physical impairment, and gastrointestinal bleeding risks when using gastrointestinal protectants, NSAIDS, or corticosteroids), users of ticlopidine showed an increased risk of hospitalization for bleeding episodes compared to nonusers of ticlopidine (odds ratio, 1.07; 95% CI, 0.86 to 1.34). For comparison, the adjusted rate of hospitalizations for aspirin users due to bleeding was an odds ratio of 1.07 (95% CI, 0.96 to 1.18).

Racial groups

Direct evidence

In the PRoFESS trial, overall, the fixed-dose combination of extended-release dipyridamole plus aspirin did not meet predefined criteria for noninferiority compared with clopidogrel for the primary outcome of recurrent stroke. The relative difference between the antiplatelet agents was consistent across subgroups based on ethnicity in patients with recent ischemic stroke (African, Chinese, South Asian, Other Asian, white/European, Native Latin).[42]

No other head-to-head trials of newer antiplatelet agents in other included populations reported subgroup analyses based on race.

Indirect evidence

There was little evidence to suggest that the newer antiplatelet agents differ in effect or tolerance across ethnic groups. One study[45] of African American stroke patients evaluated ticlopidine monotherapy to aspirin monotherapy and reported a similar benefit in each group in the prevention of recurrent stroke, myocardial infarction, or vascular death and a similar frequency of adverse effects compared to other studies. One of the 902 ticlopidine treated patients appeared to develop thrombocytopenia, with a possible diagnosis of thrombotic thrombocytopenic purpura.

In a subgroup analysis of the ESPRIT[48] trial, compared to aspirin alone, there was a trend toward increased benefit with the fixed-dose combination of extended-release dipyridamole plus aspirin on the primary composite outcome regardless of country (Asian compared with non-Asian).

Gender

Direct evidence

TRITON-TIMI 38 reported Kaplan-Meier estimated hazard ratios for selected subgroups of patients for the primary composite endpoint (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). No statistically significant interaction was found between sex and the relative effect of prasugrel compared with clopidogrel. The overall hazard ratio for prasugrel compared with clopidogrel was 0.81. The hazard ratio for men was very close at 0.80, while at 0.87, the hazard ratio for women was weaker and no longer statistically significant, likely due to the smaller sample size (n=3523).[25]

In the PRoFESS trial overall, the fixed-dose combination of extended-release dipyridamole plus aspirin did not meet predefined criteria for noninferiority compared with clopidogrel for the primary outcome of recurrent stroke. The relative difference between

antiplatelet agents was consistent in subgroups of men (9.3% compared with 9.3%) or women (8.5% compared with 7.9%) with recent ischemic stroke.[42]

Indirect evidence

No studies yet indicate that men and women have different outcomes in primary events when using the newer antiplatelet agents. The majority of the studies included mostly male populations. A good-quality meta-analysis of blinded randomized controlled trials evaluated the relative effectiveness of clopidogrel plus aspirin to aspirin alone in subgroups of men and women using a random effects model.[70] This meta-analysis pooled data from 5 trials, including CREDO, CURE, CLARITY, COMMIT, and CHARISMA. However, because our review did not include CLARITY or COMMIT, we pooled the event data provided by Berger, et al. for CREDO, CURE, and CHARISMA alone for the outcomes of all-cause mortality and major bleeding. As can be seen in Table 5, clopidogrel significantly increased risk of major bleeding in both men and women and did not significantly reduce risk of all-cause mortality in either subgroup.

Table 5. Clopidogrel plus aspirin compared with aspirin alone: Pooled relative risks (95% confidence intervals) for outcomes from CREDO, CURE, and CHARISMA

	All-cause mortality	Major bleeding
Men	0.93 (0.82 to 1.05)	1.25 (1.06 to 1.48)
Women	1.00 (0.85 to 1.15)	1.49 (1.17 to 1.90)

In TASS,[46] the beneficial effects of ticlopidine in reducing the risk of nonfatal stroke or death were observed in both men and women.

In the ESPS-2[47] trial, 42% of the study population was women. No gender difference in efficacy or tolerability was noted.

In a subgroup analysis of the ESPRIT[48] trial, compared to aspirin alone, there was a trend toward increased benefit with the fixed-dose combination of extended-release dipyridamole plus aspirin on the primary composite outcome both in men and women.

Comorbidities

Direct evidence

Few head-to-head trials reported subgroup analyses based on comorbidities. The TRITON-TIMI 38 trial reported Kaplan-Meier estimated hazard ratios for subgroups of patients with and without diabetes for the primary composite endpoint (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). No statistically significant interaction was found between presence of diabetes and the relative effectiveness of prasugrel compared with clopidogrel. The benefit of prasugrel over clopidogrel was significant both in patients with diabetes (hazard ratio, 0.87) and without diabetes (hazard ratio, 0.72).[25] The authors performed a series of post-hoc exploratory analyses to identify subgroups of patients who did not have a favorable net clinical benefit. Net benefit (presumably hazard ratio <1) or net harm (presumably hazard ratio >1) was defined as the rate of death from any cause, nonfatal myocardial infarction, nonfatal stroke, or non-coronary artery bypass graft-related nonfatal major bleeding. Patients

who had a previous stroke of transient ischemic attack had net harm from prasugrel (hazard ratio, 1.54; 95% CI, 1.02 to 2.32; *P*=0.04). Patients weighing less than 60 kg had no net benefit from prasugrel (hazard ratio, 1.03; 95% CI, 0.69 to 1.53; *P*=0.89).

In 20 332 patients with recent ischemic stroke who participated in the good-quality PRoFESS trial,[42] the fixed-dose combination of extended-release dipyridamole plus aspirin did not meet predefined criteria for noninferiority compared with clopidogrel for the primary outcome of recurrent stroke. The relative difference between antiplatelet agents was consistent in subgroups of patients with obesity (8.7% compared with 9.1%) or without obesity (9.0% compared with 8.8%) and with diabetes mellitus (10.7% compared with 11.8%) or without diabetes mellitus (10.7% compared with 11.8%).

One fair-quality, head-to-head trial that compared clopidogrel 75 mg and ticlopidine 200 mg in Japanese patients with prior stroke for 52 weeks provided insufficient data to determine how the relative difference between the 2 drugs was impacted for the outcome of any recurrent cardiovascular events.[41] When multivariate analysis was performed using combined data from the clopidogrel and ticlopidine groups, the presence of diabetes (adjusted hazard ratio, 2.6; 95% CI, 1.3 to 5.5) led to a significant increased risk of any recurrent cardiovascular event, whereas the presence of hyperlipidemia led to a significant decrease in risk (adjusted hazard ratio, 0.36; 95% CI, 0.15 to 0.87). No comparison of clopidogrel and ticlopidine in patient subgroups based on diabetes or hyperlipidemia status was reported, however.

Indirect evidence

In a subset analysis[21] of CURE, patients with diabetes had a lower incidence of the first primary outcome on clopidogrel plus aspirin than placebo plus aspirin (14.2% compared with 16.7%, respectively). Likewise, patients without diabetes also had a lower incidence of the first primary outcome with clopidogrel plus aspirin than placebo plus aspirin (7.9 compared with 9.9%, respectively). Patients with diabetes had higher event rates than nondiabetics but within the diabetic group, those on clopidogrel plus aspirin showed a benefit compared to placebo plus aspirin.

In several prespecified subgroup analyses using the primary endpoint in the CHARISMA[23] trial, patients with and without a history of diabetes, hypertension, hypercholesterolemia, stroke, prior coronary artery bypass graft surgery or percutaneous coronary intervention, or prior myocardial infarction were evaluated. In addition to these groups, current smoking, body mass index, gender, and age were also included in the analyses. All subgroups, except patients with no history of myocardial infarction or coronary artery bypass graft surgery and patients with a 30 or greater body mass index score fared better with clopidogrel plus aspirin than aspirin alone as represented by the hazard ratios for each subgroups (see also gender section). Of note, in the total study population, 75.6% of the patients had an abnormal body mass index; 42.2% were overweight and 33.4% were obese.[71] Diabetes was prevalent in 42% of the study population. Hazards ratios for other subgroups mentioned in the text including patients with and without peripheral arterial disease or prior transient ischemic attack were not depicted.

In ESPS-2, rates of first stroke (fatal and nonfatal) were evaluated in subgroups of patients with noninsulin-dependent diabetes mellitus and insulin-dependent diabetes mellitus. In patients with noninsulin-dependent diabetes mellitus, compared to taking aspirin alone, rate of first stroke was slightly higher with the fixed-dose combination of extended-release

dipyridamole plus aspirin (12.3% compared with 11.0%). However, comparative statistics within subgroups were not provided.

A post-hoc analysis[72] of the ESPS-2 was conducted to evaluate the reduction in risk for recurrent stroke in various subgroups taking aspirin plus extended-release dipyridamole (n=1650) compared with aspirin alone (n=1649). The analysis used external stroke validated models from the Framingham Study and the Stroke Prognostic Instrument II (SPI-2) to estimate the risk. Estimated risk categories based on the ESPS-2 baseline variables were converted to risk scores using these 2 models. Compared with aspirin alone, treatment with extended-release dipyridamole/aspirin resulted in substantial relative hazard reductions for stroke within some of the specific risk factor subgroups including those younger than 70 years of age, those with hypertension, prior myocardial infarction, prior stroke or transient ischemic attack, and any prior cardiovascular disease, and current smokers. The greatest relative hazard reduction for stroke or vascular events was among patients who already had experienced a stroke or transient ischemic attack before the qualifying event. Those who already had at least 2 prior events (transient ischemic attack/stroke), of which 1 was the qualifying events for inclusion into the study, had the least incidence of subsequent stroke compared to those who had only 1 prior event (the qualifying transient ischemic attack/stroke). Patients with a history of myocardial infarction who were treated with extended-release dipyridamole/aspirin had a 36.8% relative hazard reduction for stroke compared with those taking aspirin alone. Patients with any prior cardiovascular disease had a 27.3% relative hazard reduction while taking extended-release dipyridamole/aspirin compared with 18.2% relative hazard reduction in those that did not have a history of prior cardiovascular disease. Patients taking extended-release dipyridamole/aspirin had a greater relative hazard reduction for the endpoint of combined stroke or vascular events among those patients with a prior stroke or transient ischemic attacks, previous myocardial infarction, and among current smokers. Sacco, et al.[72] then conducted the analysis stratifying patients at low and high risk for recurrent stroke using the baseline ESPS-2 cohort that had been categorized according to the Framingham stroke risk score or the SPI-2 score as depicted in Table 6. The annual risk for recurrent stroke among those treated with aspirin increased from 3.8% in the low-risk group to 10.1% in the high-risk group for the Framingham score and from 3.7% to 13.2% for the SPI-2 score. Relative hazard reductions favored the combination of aspirin plus extended-release dipyridamole in all the subgroups, and were greatest for the high-risk Framingham group and the moderate-risk SPI-2 subgroup. Similar results were observed for stroke or vascular events. The post-hoc analysis suggested that extended-release dipyridamole/aspirin provides greater benefit for patients with a higher risk for stroke, as per predicted stroke probabilities.

Table 6. Stroke or vascular event rates in ESPS-2: extended-release dipyridamole/aspirin or aspirin monotherapy[72]

Risk group	Number of subjects	With extended-release dipyridamole/aspirin[a]	With aspirin[a] only	Relative hazard reduction (CL)	*P* values
Annual stroke rates					
Framingham stroke risk score					
Low	1453	3.4	3.8	12.3 (-30.4, 41.0)	0.52
High	1743	7.0	10.1	30.2 (10.3, 45.7)	0.005
SPI-2 risk score					
Low	1426	3.2	3.7	11.8 (-32.9, 41.4)	0.55
Moderate	1471	6.3	9.6	34.3 (12.8, 50.5)	0.004
High	299	10.9	13.2	17.2 (-39.3, 50.8)	0.48
Annual stroke or vascular event rates					
Framingham stroke risk score					
Low	1453	4.1	5.0	17.4 (-17.8, 42.1)	0.29
High	1743	11.4	14.3	20.6 (2.7, 35.2)	0.03
SPI-2 risk score					
Low	1426	4.2	4.9	13.8 (-23.3, 39.7)	0.42
Moderate	1471	9.5	13.1	27.5 (8.1, 42.7)	0.008
High	299	19.8	21.5	7.6 (-37.9, 38.1)	0.70

Adapted from Sacco, et al.[72]
Abbreviations: CL, confidence limit For Framingham Study model: the 10-year stroke probability (primarily first stroke) is low (≤0.15) or high (>0.15) using the following variables: age, systolic blood pressure, anti-hypertensive therapy, diabetes mellitus, cigarette smoker, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy; SPI-2, classified as low (0-3), middle (4-7), or high (8-15) using the following variables: congestive heart failure, diabetes mellitus, prior stroke, older than 70 years, stroke for enrollment event, severe hypertension, and coronary artery disease.
[a] Data are given as annual percentage of subjects in each group who experienced a stroke.

Other Medications

Proton pump inhibitors

We found no head-to-head trials that directly compared different newer antiplatelet agents in subgroups of patients based on proton pump inhibitor use. Indirect evidence of the effects of individual newer antiplatelet agents taken with or without a proton pump inhibitor was found only for prasugrel and clopidogrel.

Outcomes with concurrent use of clopidogrel and proton pump inhibitors were evaluated in 1 randomized controlled trial[73] and numerous observational studies.[74-90] We found 1 randomized controlled trial that was prospectively designed to evaluate the concomitant use of proton pump inhibitors and newer antiplatelet agents.[73] In the Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT), a total of 3873 patients with an indication for long-term dual antiplatelet therapy with aspirin and clopidogrel (e.g., acute coronary syndrome or undergoing placement of a coronary stent) were randomized to treatment with an investigational fixed-dose combination product containing clopidogrel 75 mg and omeprazole 20 mg (CGT-2168) plus aspirin or to treatment with placebo plus clopidogrel and aspirin. However, because the fixed-dose combination product was not yet approved for use in the United States or Canada

at the time of this review, we did not include or fully appraise the quality or results of COGENT and did not draw any conclusions about its findings.

Many observational studies have examined whether the cardiovascular effectiveness of clopidogrel is decreased in patients taking a proton pump inhibitor.[74-84] However, as observational studies were included in our review only to evaluate harms and not effectiveness outcomes, we did not fully evaluate the quality or results of these studies. But, according to the Expert Consensus Document released in November 2010 by the American College of Cardiology Foundation (ACCF) Task Force,[91] some studies[77-80, 84] found a significant increase in risk of various composite cardiovascular endpoints with concomitant proton pump inhibitor use that ranged from an odds ratio of 1.25 (95% CI, 1.11 to 1.41; death or rehospitalization for myocardial infarction or unstable angina)[79] to 1.95 (95% CI, 1.09 to 3.49; myocardial infarction, target vessel failure, or death).[78] In contrast, other studies found no significant difference in cardiovascular outcomes with or without use of a proton pump inhibitor.[74-76, 81-83]

We identified 9 observational studies that evaluated the potential benefit of taking a proton pump inhibitor to reduce clopidogrel-related gastrointestinal bleeding.[74, 75, 82, 85-90] Four observational studies evaluated bleeding outcomes with concurrent use of clopidogrel and proton pump inhibitors in broadly-defined patient populations with average risk of gastrointestinal bleeding.[74, 75, 82, 85] Two were good-quality large-scale, population-based cohort studies,[75, 82] 1 was a post-hoc, observational analysis of patients in each arm of the TRITON-TIMI 38 trial,[74]and 1 was a small, cohort study of patients from a single university hospital.[85] The small cohort study was rated poor quality because it had significant differences in clinical characteristics between groups at baseline, but conducted no statistical analysis to adjust for these potential confounders. Its results will not be discussed here.

The 2 good-quality cohort studies had somewhat consistent results regarding effects of proton pump inhibitor use on overall gastrointestinal bleeding outcomes.[75, 82] The first cohort study used data from the Danish National Patient Registry to identify 56 406 patients discharged after first-time myocardial infarction with a prescription for clopidogrel.[75] When a time-dependent, propensity score-matched, Cox proportional hazards regression analysis was performed (N=13 112), the reduction in risk for any gastrointestinal bleeding in patients receiving a proton pump inhibitor compared to those not receiving a proton pump inhibitor did not reach statistical significance (hazard ratio, 0.82; 95% CI, 0.63 to 1.07). Specific sources of gastrointestinal bleeding were not evaluated separately. The second cohort study included data from 20 596 Tennessee Medicaid program enrollees who received clopidogrel after hospitalization for coronary artery revascularization (65%), myocardial infarction (30%), or unstable angina (5%).[82] A regression model was used to adjust for multiple baseline and time-dependent variables, as well as propensity score deciles. Compared to nonusers of a proton pump inhibitor, the hazard ratio associated with concurrent proton pump inhibitor use for risk of hospitalization for gastroduodenal bleeding was 0.50 (95% CI, 0.39 to 0.65) and was 0.99 (95% CI, 0.67 to 1.47) for other types of gastrointestinal bleeding. Although overall gastrointestinal bleeding was not evaluated, considering the hazard ratio would likely fall somewhere between those found for the gastroduodenal (0.50) and other bleeding (0.99) outcomes, it appears possible that results of such an analysis would be similar to findings from the Danish cohort study.

Data from the TRITON-TIMI 38 trial was used to conduct a post-hoc analysis of the association between using a proton pump inhibitor and clinical outcomes for patients that were treated with clopidogrel or prasugrel.[74] Although the primary analysis of TRITON-TIMI 38 trial involved direct comparison of clopidogrel and prasugrel, for the post-hoc analysis of proton

pump inhibitor use, each arm of the trial was treated as a separate cohort and was not compared to one another. Gastrointestinal bleeding was not reported, but for major, noncoronary artery bypass graft surgery-related, use of a proton pump inhibitor did not have a significant effect in the clopidogrel arm (adjusted hazard ratio, 1.20; 95% CI, 0.80 to 1.7) or in the prasugrel arm (adjusted hazard ratio, 0.97; 95% CI, 0.67 to 1.39).

The remaining 5 observational studies involved patients with prior gastrointestinal bleeding who are at the highest risk for recurrent bleeding on antiplatelet therapy (Table 7).[86-90] However, in 2 of the studies, evaluation of the association between concurrent use of clopidogrel and proton pump inhibitors and bleeding risk is potentially confounded by concomitant therapy with aspirin.[89, 90] In another 2 studies, use of proton pump inhibitors is considered in combination with thienopyridines as a group and it is not possible to separate out the effects of any individual thienopyridine.[86, 87] Therefore, only 1 study was eligible for evaluating the gastroprotective benefit of proton pump inhibitor use in high-risk patients with a history of hospitalization for gastrointestinal complications before the initiation of clopidogrel.[88] Data were obtained from the Taiwanese National Health Insurance database for 2626 patients prescribed clopidogrel, with or without a proton pump inhibitor. Medical history included stroke for 35%, myocardial infarction for 19%, percutaneous transluminal coronary angioplasty for 13%, and coronary artery bypass graft for 1%. Based on results of a Cox proportional hazards analysis that was adjusted using a propensity score, use of a proton pump inhibitor was not associated with a significant reduction in risk of recurrent hospitalization for major gastrointestinal complications (1.08; 95% CI, 0.89 to 1.33).

Table 7. Gastrointestinal outcomes with concomitant proton pump inhibitor use in observational studies of high-risk patients

Author Year	Treatment	Sample size	Outcome: PPI compared with no PPI
Hsiao 2009	Clopidogrel	PPI=590 No PPI=2036	Recurrent major GI complications: HR, 1.08 (0.89 to 1.33)
Ng 2008	Aspirin plus clopidogrel	PPI=213 No PPI=774	Upper GI bleeding: OR, 0.04 (0.002 to 0.21)
Ng 2003	Aspirin plus clopidogrel	N=70	Rebleeding 0% vs. 29.5%; *P*=0.057
Chin 2007	Thienopyridine	Cases=67 Controls=201	Upper GI bleeding: OR, 0.08 (0.02 to 0.40)
Lanas 2007	Clopidogrel/ticlopidine	Cases=239 Controls=732	Peptic ulcer bleeding: RR, 0.19 (0.07 to 0.49)

Abbreviations: GI, gastrointestinal; HR, hazard ratio; OR, odds ratio; PPI, proton pump inhibitor; RR, relative risk.

Warfarin

Three observational studies met criteria for evaluation of whether risk of bleeding with newer antiplatelet agents was exacerbated in patients with additional indications for treatment with warfarin.[92-94] Results from 2 studies were not discussed here, however, as they were rated poor quality due to having high risks of both selection and ascertainment biases and both lacked analyses controlling for potentially confounding variables.[92, 93] The remaining population-based cohort study was good quality and used data from the Danish National Patient Register to evaluate bleeding risk in patients who had been hospitalized for first-time myocardial infarction

and who had a prescription within 90 days of discharge for either monotherapy with aspirin, clopidogrel, or a Vitamin K antagonist; dual therapy with aspirin plus clopidogrel, aspirin plus a Vitamin K antagonist, or clopidogrel plus a Vitamin K antagonist; or triple therapy with aspirin, clopidogrel, and a Vitamin K antagonist.[94] Men accounted for 63% of the population and the mean age was 65.3 years for men and 72.6 years for women. Sample sizes, treatment duration, and incidence of nonfatal and fatal bleeding events for the treatment groups of interest are provided in Table 8. Although Cox proportional hazard analyses were performed to adjust for numerous confounding variables, aspirin monotherapy was used as the reference group and no direct comparisons of the Vitamin K antagonist alone group to the clopidogrel plus Vitamin K antagonist or triple therapy groups were reported. Compared to the Vitamin K antagonist alone group, the unadjusted incidence of nonfatal and fatal bleeding was almost 3 times greater in the groups taking a Vitamin K antagonist and clopidogrel with or without aspirin. Compared to aspirin alone, the adjusted hazard ratio was 1.23 (95% CI, 0.94 to 1.61) for Vitamin K antagonist alone, 3.52 (95% CI, 2.42 to 5.11) for clopidogrel plus Vitamin K antagonist, and 4.05 (95% CI, 3.08 to 5.33) for clopidogrel and aspirin plus Vitamin K antagonist. As the upper bound of the 95% confidence interval for the Vitamin K antagonist alone group (1.61) does not overlap with the lower bounds of the 95% confidence intervals for the dual and triple therapy groups (2.42 and 3.08, respectively), a high likelihood of a significant increase in risk of bleeding when clopidogrel is added to a Vitamin K antagonist was indicated.

Table 8. Nonfatal and fatal bleeding events in Sorensen 2009[94]

Treatment	N	Duration of treatment (days)	Unadjusted incidence (% per person-year)
Vitamin K antagonist alone	1320	161	4.3%
Clopidogrel plus vitamin K antagonist	196	108	12.3%
Aspirin, clopidogrel, and vitamin K antagonist	315	155	12.0%

Genotype

We found no eligible randomized controlled trials designed to assess the effectiveness of clopidogrel in subgroups of patients based on genotype. We included 2 studies to evaluate the potential effects of certain genotypes on bleeding outcomes in patients taking clopidogrel[95, 96] or prasugrel.[95] The first is fair-quality observational study that assessed the impact of the cytochrome P450 (CYP) 2C19*17 “gain-of-function” allele on risk of bleeding events in clopidogrel-treated patients with coronary stent placement.[96] This study included 1524 patients from a single center in Munich, Germany who underwent percutaneous coronary intervention and were pretreated with a loading dose of 600 mg clopidogrel and discharged with a dual antiplatelet regimen of 75 mg clopidogrel and 100 mg aspirin. 902 patients (59%) were wild-type homozygous for the *17 allelic variant (wt/wt) and 622 were carriers of at least one *17 allele (wt/*17 or *17/*17). For major bleeding alone (Thrombolysis in Myocardial Infarction [TIMI]

criteria) at 30 days, there was no significant difference between carriers of the CYP2C19*17 allele and noncarriers (odds ratio, 2.04; 95% CI, 0.68 to 6.12).

The second study evaluated whether the effects of clopidogrel and prasugrel were reduced in individuals who are *ABCB1* 3435 TT homozygotes compared with individuals who were either *ABCB1* 3435 CC homozygotes or *ABCB1* 3435 CT heterozygotes.[95] This observational study used data from 1471 of 6795 (22%) patients in the clopidogrel arm and 1461 of 6813 (21%) patients in the prasugrel arm of the TRITON-TIMI 38 trial who provided samples for genetic analysis.[95] Although the primary analysis of the TRITON-TIMI 38 trial involved the direct comparison of clopidogrel and prasugrel,[25] this genetic substudy evaluated each group of patients as separate cohorts.[95] Patients with the *ABCB1* 3435 TT genotype comprised 27% of the study sample and those without comprised the other 73% (*ABCB1* 3435 CC or CT genotypes). Rates of major bleeding were not reported separately. For the combined rate of TIMI major or minor bleeding, there was no significant difference between patients with the *ABCB1* 3435 TT genotype and those without in either the clopidogrel cohort (hazard ratio, 1.49; 95% CI, 0.79 to 2.82) or the prasugrel cohort (hazard ratio, 1.50; 95% CI, 0.86 to 2.62).

Both studies also evaluated the potential effects of genotype variants on the cardiovascular effectiveness of clopidogrel and prasugrel. However, as observational studies were included in our review only to evaluate harms and not effectiveness outcomes, we did not fully evaluate the results for the cardiovascular outcomes.

SUMMARY

Strength of Evidence

The results of this review are summarized in Table 9, below, and Appendix F summarizes the strength of the evidence for each key question. High-strength, comparative evidence was found only for effectiveness outcomes for the comparison of prasugrel and clopidogrel following coronary revascularization and for the comparison of the fixed-dose combination of extended-release dipyridamole plus aspirin and clopidogrel following recent stroke or transient ischemic attack. Evidence of the direct comparison between ticlopidine and clopidogrel was available in patients undergoing coronary interventions and following a recent stroke or transient ischemic attack, but was generally of moderate to low strength. No direct comparative data was available in patients with acute coronary syndromes or peripheral vascular disease. For evaluation of differences based on duration of therapy, evidence was generally moderate strength but limited to the question of whether 6 to 12 months of clopidogrel treatment was better than 1 month following coronary interventions. For subgroups based on age, race, and sex, evidence was generally low strength and came primarily from subgroup analyses of the primary composite effectiveness outcomes from head-to-head trials of prasugrel and clopidogrel following coronary revascularization and of the fixed-dose combination of extended-release dipyridamole plus aspirin and clopidogrel following recent stroke or transient ischemic attack. For evaluation of concomitant use of proton pump inhibitors in patients taking clopidogrel, evidence came primarily from observational studies. However, as observational studies were included in our review only to evaluate harms and not effectiveness outcomes, these studies only provided low- to moderate-strength evidence for evaluation of gastrointestinal bleeding risk and insufficient evidence to draw conclusions about risk of cardiovascular events.

Limitations of this Report

As with other types of research, the limitations of this systematic review are important to recognize. These can be divided into 2 groups, those relating to generalizability of the results and those relating to methodology within the scope of this review. The generalizability of the results were limited by the scope of the key questions, inclusion criteria, and by the generalizability of the studies included. Most studies included narrowly defined populations of patients who met strict criteria for case definition, had fewer comorbidities, and used fewer concomitant medications. Minorities, female patients, and the most seriously ill patients were under represented.

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies. Few direct head-to-head comparisons of the included drugs have been conducted for acute coronary syndrome and peripheral arterial disease, which limits our conclusions to indirect comparison of placebo-controlled trials for many of the outcomes. This limits the strength of the evidence due to heterogeneity of trial populations, interventions, and outcomes assessment.

Applicability

One potential limitation to the applicability of the findings of this review is that they relate to a narrower range of drugs than are available in clinical practice. The selection of drugs included in this review was influenced by the specific programmatic interests of the organizations participating in the Drug Effectiveness Review Project and are not meant to be read as a usage guideline. Of the drugs studied, trials differed with respect to dosing regimens limiting any conclusions about optimal dose.

Studies Pending Review

We identified no trials in progress that would meet inclusion criteria for this review and would potentially change conclusions.

Table 9. Summary of the evidence

Key Question	Strength of evidence	Conclusion
Key Question 1. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in effectiveness?		
ACS medically managed	Clopidogrel/aspirin vs. placebo/aspirin: Moderate	No difference between placebo/aspirin and clopidogrel/aspirin at reducing all-cause mortality and cardiovascular mortality at 12 months
	Clopidogrel/aspirin vs. placebo/aspirin: Moderate	Significant difference in reduction of MI at 12 months
	Clopidogrel/aspirin vs. placebo/aspirin: Low	No significant difference in reduction of cardiovascular mortality at median 28 months
	Clopidogrel vs aspirin: Low	No significant difference in reduction of cardiovascular mortality at mean 1.9 years

Key Question	Strength of evidence	Conclusion
ACS coronary interventions	Prasugrel/aspirin vs. clopidogrel/aspirin: High	Prasugrel reduces risk of target-vessel revascularization at 15 months when compared to clopidogrel
	Prasugrel/aspirin vs. clopidogrel/aspirin: Mod-High	No difference in risk of all-cause mortality and cardiovascular mortality at 15 months
	Ticlopidine/aspirin vs. clopidogrel/aspirin: Low-Moderate	No difference in risk of target-vessel revascularization at 30 days and 6 months
	Ticlopidine/aspirin vs. clopidogrel/aspirin: Low	No difference in risk for cardiovascular mortality at 30 days
Stroke/transient ischemic attack	Extended-release dipyridamole/aspirin vs. clopidogrel: High	No significant difference for all-cause mortality, cardiovascular mortality, and recurrent stroke
	Clopidogrel vs. ticlopidine: Moderate	No significant difference for all-cause mortality, cardiovascular mortality or cerebral infarction
Peripheral vascular disease	Clopidogrel vs. aspirin: Moderate	No significant difference for cardiovascular mortality
	Clopidogrel plus aspirin vs. aspirin alone: Low	No significant difference for all-cause mortality, cardiovascular mortality, and revascularization
Key Question 2. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in harms?		
ACS medically managed	Clopidogrel/aspirin vs. placebo/aspirin: Moderate	Increased risk of major bleeding at 12 months
ACS coronary interventions	Prasugrel/aspirin vs. clopidogrel/aspirin: Moderate	Increased risk of major bleeding with prasugrel and no difference in withdrawal due to adverse events at 15 months
	Ticlopidine/aspirin vs. clopidogrel/aspirin: Moderate	No difference in risk of major bleeding at 28 days
	Ticlopidine/aspirin vs. clopidogrel/aspirin: Low	Increased withdrawals due to adverse events with ticlopidine and no difference in risk of major bleeding at 6 months
Stroke/transient ischemic attack	Extended-release dipyridamole/aspirin vs. clopidogrel: Moderate to high	Lower rate of major bleeding and withdrawal due to adverse events with clopidogrel
	Clopidogrel vs. ticlopidine: Moderate	Lower rate of neutropenia and withdrawals due to adverse events with clopidogrel and no significant difference in rate of major bleeding
Peripheral vascular disease	Clopidogrel vs. aspirin: Insufficient	No data for peripheral arterial disease subgroup
	Clopidogrel plus aspirin vs. aspirin alone: Low	No significant difference for major bleeding
Key Question 3. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in effectiveness and harms based on duration of therapy?		
ACS coronary interventions	Clopidogrel 1 month vs. clopidogrel 6 months: Moderate	Significantly lower risk of revascularization with 6 months of therapy, no significant increase in bleeding risk, and nonsignificant benefit for all-cause mortality and cardiovascular mortality
	Clopidogrel 1 month vs. clopidogrel/average 8 months: Moderate	Smaller, nonsignificant benefit for revascularization with 8 months of therapy compared with 1 month and a trend toward increase in bleeding risk
	Clopidogrel 1 month vs. Clopidogrel 12 months: Low	Further reduction in benefit for revascularization with 12 months of therapy and further, but nonsignificant increase in risk of bleeding

Key Question	Strength of evidence	Conclusion
Key Question 4. Are there subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one antiplatelet agent is more effective or associated with fewer harms?		
Demographics	Clopidogrel vs. prasugrel, fixed-dose combination of extended-release dipyridamole plus aspirin vs. clopidogrel: Low	There was no significant interaction between age or sex and the relative effects of prasugrel and clopidogrel on the primary composite endpoint (death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke) The fixed-dose combination of extended-release dipyridamole plus aspirin did not meet predefined criteria for noninferiority compared with clopidogrel for the primary outcome of recurrent stroke across all patients in the PRoFESS trial, and the relative difference between antiplatelet agents was consistent across subgroups based on age, race, and sex
Comorbidities	Clopidogrel vs. prasugrel, fixed-dose combination of extended-release dipyridamole plus aspirin vs clopidogrel: Low	There was no significant interaction between presence of diabetes and the relative effects of prasugrel and clopidogrel on the primary composite endpoint (death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke) The fixed-dose combination of extended-release dipyridamole plus aspirin did not meet predefined criteria for noninferiority compared with clopidogrel for the primary outcome of recurrent stroke across all patients in the PRoFESS trial, and the relative difference between antiplatelet agents was consistent across subgroups of patients with diabetes or obesity
Other medications	Clopidogrel plus warfarin: Low	Compared with Vitamin K antagonist alone (4.3%), risk of fatal and nonfatal bleeding increased when combined with clopidogrel (12.3%) and clopidogrel plus aspirin (12.0%)
	Clopidogrel plus proton pump inhibitors: Insufficient for benefit-to-risk ratio; insufficient for cardiovascular effectiveness; low to moderate for gastrointestinal bleeding	We found no eligible randomized controlled trials to assess whether concomitant use of a proton pump inhibitor increases the risk of cardiovascular events in patients taking clopidogrel Compared to nonuse, there was moderate strength evidence that use of a proton pump inhibitor in average-risk patients taking clopidogrel (without aspirin) significantly reduces risk of hospitalization due to gastroduodenal bleeding There was low-strength evidence that proton pump inhibitor use does not significantly reduce composite risk of any gastrointestinal bleeding event either in average-risk or high-risk populations
Genotype	Clopidogrel, prasugrel: Low	Compared to CYP2C19*17 noncarriers, carriers of the CYP2C19*17 allele did not have a significantly greater risk of major bleeding during treatment with clopidogrel Carriage of the ABCB1 3435 TT genotype also does not significantly impact the combined risk of major or minor bleeding in patients taking either clopidogrel or prasugrel

Abbreviations: ACS, acute coronary syndrome; MI, myocardial infarction.

CONCLUSIONS

High-strength evidence indicated that in coronary revascularization, prasugrel reduces target-vessel revascularization more than clopidogrel at 15 months, while moderate-strength evidence indicated that there was more major bleeding with prasugrel. Evidence was moderate strength that the use of clopidogrel for 6 months after coronary revascularization resulted in lower risk of revascularization compared with 1 month, with no increase in bleeding (moderate strength). The benefit lessened after 8 and 12 months and bleeding risk gradually increased (moderate to low strength). In patients with acute coronary syndrome who are managed medically, there was moderate-strength evidence of no significant difference in reduction of mortality out to at least 12 months, significantly fewer myocardial infarctions and increased major bleeding between clopidogrel plus aspirin compared with aspirin alone.

Following stroke or transient ischemic attack, high-strength evidence indicated that extended-release dipyridamole plus aspirin did not meet criteria for being noninferior to clopidogrel for the primary outcome of recurrent stroke and had higher risks of major bleeding and withdrawals due to adverse events.

Evidence was insufficient to draw strong conclusions about the benefit-risk ratio of using a proton pump inhibitor for any patients taking clopidogrel.

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Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An **adverse event** for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intent to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intent to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intent-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B. Boxed warnings for included drugs[1-3]

Generic name	Trade name	Black box warnings
Clopidogrel	Plavix®	WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 *[see Warnings and Precautions (5.1)]*. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy *[see Clinical Pharmacology (12.5)]*. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers *[see Dosage and Administration (2.3)]*.
Prasugrel	Effient®	**WARNING: BLEEDING RISK** Effient can cause significant, sometimes fatal, bleeding *[see Warnings and Precautions (5.1 and 5.2) and Adverse Reactions (6.1)]*. Do not use Effient in patients with active pathological bleeding or a history of transient ischemic attack or stroke *[see Contraindications (4.1 and 4.2)]*. In patients ≥ 75 years of age, Effient is generally not recommended, because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI) where its effect appears to be greater and its use may be considered *[see Use in Specific Populations* (*8.5)]*. Do not start Effient in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Effient at least 7 days prior to any surgery. Additional risk factors for bleeding include: • body weight < 60 kg • propensity to bleed • concomitant use of medications that increase the risk of bleeding (*e.g.*, warfarin, heparin, fibrinolytic therapy, chronic use of nonsteroidal anti-inflammatory drugs [NSAIDS]) Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Effient. If possible, manage bleeding without discontinuing Effient. Discontinuing Effient, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events *[see Warnings and Precautions (5.3)]*.
Ticlopidine	Generic only	Warning Ticlopidine hydrochloride can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis and thrombotic thrombocytopenic purpura (TTP) Neutropenia/Agranulocytosis Among 2048 patients in clinical trials, there were 50 cases (2.4%) of neutropenia (less than 1200 neutrophils/mm^3), and the neutrophil

Generic name	Trade name	Black box warnings
		count was below 450/mm3 in 17 of these patients (0.8% of the total population). TTP One case of thrombotic thrombocytopenic purpura was reported during clinical trials. Based on postmarketing data, US physicians reported about 100 cases between 1992 and 1997. Based on an estimated patient exposure of 2 million to 4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated TTP may be as high as one case in every 2000 to 4000 patients exposed. Monitoring of clinical and hematological status Severe hematological adverse reactions may occur within a few days of the start of therapy. The incidence of TTP peaks after about 3 to 4 weeks of therapy and neutropenia peaks at approximately 4 to 6 weeks with both declining thereafter. Only a few cases have arisen after more than 3 months of treatment. Hematological reactions cannot be reliably predicted by any identified demographic or clinical characteristics. During the first 3 months of treatment, patients receiving ticlopidine hydrochloride must therefore be hematologically and clinically monitored for evidence of neutropenia or TTP. If any such evidence is seen, ticlopidine hydrochloride must be immediately discontinued. The detection and treatment of ticlopidine-associated hematological adverse reactions are further described under WARNINGS.

References

1. Sanofi Aventis US. Plavix product label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020839s051lbl.pdf. Accessed May 25, 2011.
2. Eli Lilly and Co. Effient product label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022307s002lbl.pdf. Accessed May 25, 2011.
3. Ticlopidine hydrochloride product label. http://www.accessdata.fda.gov/drugsatfda_docs/anda/99/75161_Ticlopidine%20Hydrochloride_Prntlbl.pdf. Accessed May 25, 2011.

Appendix C. Search strategies for Update 2

The searches were repeated in Jan 2011 to identify additional citations.
Database: Ovid MEDLINE(R) <1996 to September Week 4 2010>
Search Strategy:
---
1 clopidogrel.mp. (4917)
2 plavix.mp. (133)
3 ticlopidine.mp. or exp Ticlopidine/ (4913)
4 dipyridamole.mp. or exp Dipyridamole/ (3133)
5 exp Aspirin/ or aspirin.mp. (21886)
6 4 and 5 (646)
7 aggrenox.mp. (24)
8 1 or 2 or 3 or 6 or 7 (6283)
9 acute coronary syndrome.mp. or exp Acute Coronary Syndrome/ (6837)
10 coronary disease.mp. or exp Coronary Disease/ (75998)
11 myocardial infarction.mp. or exp Myocardial Infarction/ (77447)
12 coronary artery bypass.mp. or exp Coronary Artery Bypass/ (27512)
13 coronary bypass.mp. (3506)
14 exp Angioplasty/ or angioplasty.mp. (38147)
15 stent.mp. or exp Stents/ (40029)
16 cerebrovascular accident.mp. or exp Stroke/ (51142)
17 transient ischemic attack.mp. or exp Ischemic Attack, Transient/ (7761)
18 peripheral vascular disease.mp. or exp Peripheral Vascular Diseases/ (14189)
19 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (248797)
20 8 and 19 (4272)
21 limit 20 to (english language and humans) (3562)
22 limit 21 to randomized controlled trial (549)
23 (201004$ or 201005$ or 201006$ or 201007$ or 201008$ or 201009$ or 201010$).ed. (361626)
24 22 and 23 (44)

Database: Ovid MEDLINE(R) <1996 to September Week 4 2010>
Search Strategy:
---
1 clopidogrel.mp. (4917)
2 plavix.mp. (133)
3 ticlopidine.mp. or exp Ticlopidine/ (4913)
4 dipyridamole.mp. or exp Dipyridamole/ (3133)
5 exp Aspirin/ or aspirin.mp. (21886)
6 4 and 5 (646)
7 aggrenox.mp. (24)
8 1 or 2 or 3 or 6 or 7 (6283)
9 acute coronary syndrome.mp. or exp Acute Coronary Syndrome/ (6837)
10 coronary disease.mp. or exp Coronary Disease/ (75998)
11 myocardial infarction.mp. or exp Myocardial Infarction/ (77447)

12 coronary artery bypass.mp. or exp Coronary Artery Bypass/ (27512)
13 coronary bypass.mp. (3506)
14 exp Angioplasty/ or angioplasty.mp. (38147)
15 stent.mp. or exp Stents/ (40029)
16 cerebrovascular accident.mp. or exp Stroke/ (51142)
17 transient ischemic attack.mp. or exp Ischemic Attack, Transient/ (7761)
18 peripheral vascular disease.mp. or exp Peripheral Vascular Diseases/ (14189)
19 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (248797)
20 8 and 19 (4272)
21 limit 20 to (english language and humans) (3562)
22 limit 21 to yr="2006 -Current" (2064)
23 (MEDLINE or systematic review).tw. or meta-analysis.pt. (56888)
24 22 and 23 (62)

Database: Ovid MEDLINE(R) <1996 to September Week 4 2010>
Search Strategy:
---
1 clopidogrel.mp. (4917)
2 plavix.mp. (133)
3 ticlopidine.mp. or exp Ticlopidine/ (4913)
4 dipyridamole.mp. or exp Dipyridamole/ (3133)
5 exp Aspirin/ or aspirin.mp. (21886)
6 4 and 5 (646)
7 aggrenox.mp. (24)
8 1 or 2 or 3 or 6 or 7 (6283)
9 acute coronary syndrome.mp. or exp Acute Coronary Syndrome/ (6837)
10 coronary disease.mp. or exp Coronary Disease/ (75998)
11 myocardial infarction.mp. or exp Myocardial Infarction/ (77447)
12 coronary artery bypass.mp. or exp Coronary Artery Bypass/ (27512)
13 coronary bypass.mp. (3506)
14 exp Angioplasty/ or angioplasty.mp. (38147)
15 stent.mp. or exp Stents/ (40029)
16 cerebrovascular accident.mp. or exp Stroke/ (51142)
17 transient ischemic attack.mp. or exp Ischemic Attack, Transient/ (7761)
18 peripheral vascular disease.mp. or exp Peripheral Vascular Diseases/ (14189)
19 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (248797)
20 8 and 19 (4272)
21 limit 20 to (english language and humans) (3562)
22 limit 21 to yr="2006 -Current" (2064)
23 ae.fs. (601779)
24 adverse.mp. (145598)
25 harm.mp. (12721)
26 safe$.mp. (275577)
27 23 or 24 or 25 or 26 (882949)
28 22 and 27 (1100)

29 limit 28 to (case reports or clinical conference or comment or consensus development conference or consensus development conference, nih or editorial or in vitro or letter or randomized controlled trial) (422)
30 28 not 29 (678)

Database: Ovid MEDLINE(R) <1996 to September Week 4 2010>
Search Strategy:
---
1 acute coronary syndrome.mp. or exp Acute Coronary Syndrome/ (6837)
2 coronary disease.mp. or exp Coronary Disease/ (75998)
3 myocardial infarction.mp. or exp Myocardial Infarction/ (77447)
4 coronary artery bypass.mp. or exp Coronary Artery Bypass/ (27512)
5 coronary bypass.mp. (3506)
6 exp Angioplasty/ or angioplasty.mp. (38147)
7 stent.mp. or exp Stents/ (40029)
8 cerebrovascular accident.mp. or exp Stroke/ (51142)
9 transient ischemic attack.mp. or exp Ischemic Attack, Transient/ (7761)
10 peripheral vascular disease.mp. or exp Peripheral Vascular Diseases/ (14189)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (248797)
12 prasugrel.mp. (306)
13 effient.mp. (4)
14 12 or 13 (306)
15 11 and 14 (196)

Database: Ovid MEDLINE(R) <1996 to September Week 4 2010>
Search Strategy:
---
1 acute coronary syndrome.mp. or exp Acute Coronary Syndrome/ (6837)
2 coronary disease.mp. or exp Coronary Disease/ (75998)
3 myocardial infarction.mp. or exp Myocardial Infarction/ (77447)
4 coronary artery bypass.mp. or exp Coronary Artery Bypass/ (27512)
5 coronary bypass.mp. (3506)
6 exp Angioplasty/ or angioplasty.mp. (38147)
7 stent.mp. or exp Stents/ (40029)
8 cerebrovascular accident.mp. or exp Stroke/ (51142)
9 transient ischemic attack.mp. or exp Ischemic Attack, Transient/ (7761)
10 peripheral vascular disease.mp. or exp Peripheral Vascular Diseases/ (14189)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (248797)
12 cilostazol.mp. (661)
13 pletal.mp. (13)
14 12 or 13 (661)
15 11 and 14 (279)
16 limit 15 to (english language and humans) (230)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2010>
Search Strategy:

---
1 acute coronary syndrome.mp. or exp Acute Coronary Syndrome/ (637)
2 stent.mp. or exp Stents/ (2657)
3 exp Coronary Artery Bypass/ (3938)
4 exp Stroke/ or stroke.mp. (14909)
5 transient ischemic attack.mp. or exp Ischemic Attack, Transient/ (643)
6 peripheral vascular disease.mp. or exp Peripheral Vascular Diseases/ (2236)
7 1 or 2 or 3 or 4 or 5 or 6 (23470)
8 cilostazol.mp. (197)
9 prasugrel.mp. (43)
10 8 or 9 (240)
11 7 and 10 (119)
12 limit 11 to yr="1996 -Current" (118)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2010>
Search Strategy:
---
1 acute coronary syndrome.mp. or exp Acute Coronary Syndrome/ (637)
2 stent.mp. or exp Stents/ (2657)
3 exp Stroke/ or stroke.mp. (14909)
4 transient ischemic attack.mp. or exp Ischemic Attack, Transient/ (643)
5 peripheral vascular disease.mp. or exp Peripheral Vascular Diseases/ (2236)
6 coronary bypass.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (929)
7 coronary artery bypass.mp. or exp Coronary Artery Bypass/ (5297)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (24861)
9 clopidogrel.mp. (819)
10 ticlopidine.mp. or exp Ticlopidine/ (1010)
11 plavix.mp. (15)
12 dipyridamole.mp. or exp Dipyridamole/ (938)
13 aspirin.mp. or exp Aspirin/ (6242)
14 12 and 13 (384)
15 aggrenox.mp. (13)
16 9 or 10 or 11 or 14 or 15 (1671)
17 8 and 16 (832)
18 limit 17 to yr="2006 -Current" (311)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 2010>
Search Strategy:
---
1 acute coronary syndrome.mp. or exp Acute Coronary Syndrome/ (44)
2 stent.mp. or exp Stents/ (87)
3 exp Stroke/ or stroke.mp. (800)
4 transient ischemic attack.mp. or exp Ischemic Attack, Transient/ (31)
5 peripheral vascular disease.mp. or exp Peripheral Vascular Diseases/ (134)
6 cilostazol.mp. (22)
7 prasugrel.mp. (5)

8 coronary bypass.mp. [mp=title, short title, abstract, full text, keywords, caption text] (25)
9 1 or 2 or 3 or 4 or 5 or 8 (938)
10 6 or 7 (26)
11 9 and 10 (21)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 2010>
Search Strategy:
---
1 acute coronary syndrome.mp. or exp Acute Coronary Syndrome/ (44)
2 stent.mp. or exp Stents/ (87)
3 exp Stroke/ or stroke.mp. (800)
4 transient ischemic attack.mp. or exp Ischemic Attack, Transient/ (31)
5 peripheral vascular disease.mp. or exp Peripheral Vascular Diseases/ (134)
6 coronary bypass.mp. [mp=title, abstract, full text, keywords, caption text] (25)
7 coronary artery bypass.mp. or exp Coronary Artery Bypass/ (82)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (960)
9 clopidogrel.mp. (45)
10 ticlopidine.mp. or exp Ticlopidine/ (34)
11 plavix.mp. (8)
12 dipyridamole.mp. or exp Dipyridamole/ (41)
13 aspirin.mp. or exp Aspirin/ (333)
14 12 and 13 (32)
15 aggrenox.mp. (1)
16 9 or 10 or 11 or 14 or 15 (56)
17 8 and 16 (47)
18 limit 17 to yr="2006 -Current" (33)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2010>
Search Strategy:
---
1 acute coronary syndrome.mp. or exp Acute Coronary Syndrome/ (52)
2 stent.mp. or exp Stents/ (152)
3 exp Stroke/ or stroke.mp. (718)
4 transient ischemic attack.mp. or exp Ischemic Attack, Transient/ (7)
5 peripheral vascular disease.mp. or exp Peripheral Vascular Diseases/ (42)
6 cilostazol.mp. (13)
7 prasugrel.mp. (1)
8 coronary bypass.mp. [mp=title, full text, keywords] (21)
9 1 or 2 or 3 or 4 or 5 or 8 (909)
10 6 or 7 (14)
11 9 and 10 (8)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2010>
Search Strategy:
---
1 acute coronary syndrome.mp. or exp Acute Coronary Syndrome/ (52)
2 stent.mp. or exp Stents/ (152)
3 exp Stroke/ or stroke.mp. (718)

4 transient ischemic attack.mp. or exp Ischemic Attack, Transient/ (7)
5 peripheral vascular disease.mp. or exp Peripheral Vascular Diseases/ (42)
6 coronary bypass.mp. [mp=title, full text, keywords] (21)
7 coronary artery bypass.mp. or exp Coronary Artery Bypass/ (246)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (1055)
9 clopidogrel.mp. (48)
10 ticlopidine.mp. or exp Ticlopidine/ (59)
11 plavix.mp. (0)
12 dipyridamole.mp. or exp Dipyridamole/ (51)
13 aspirin.mp. or exp Aspirin/ (288)
14 12 and 13 (35)
15 aggrenox.mp. (0)
16 9 or 10 or 11 or 14 or 15 (95)
17 8 and 16 (70)
18 limit 17 to last 4 years (70)

Appendix D. Excluded studies for Update 2

The following full-text publications were considered for inclusion but failed to meet the criteria for this report. See previous versions of the report on Drug Effectiveness Review Project website for studies excluded previously.

Exclusion codes: 2=ineligible outcome, 3=ineligible intervention, 4=ineligible population, 5=ineligible publication type, 6=ineligible study design

Excluded studies	Exclusion code
Head-to-head trials	
Ahn Y, Jeong MH, Jeong JW, et al. Randomized comparison of cilostazol vs clopidogrel after drug-eluting stenting in diabetic patients--clilostazol for diabetic patients in drug-eluting stent (CIDES) trial. Circulation Journal. Jan 2008;72(1):35-39.	3
Angiolillo D, Saucedo J, DeRaad R, et al. Increased platelet inhibition after switching from maintenance clopidogrel to prasugrel in patients with acute coronary syndromes: results of the SWAP (SWitching Anti Platelet) study. J Am Coll Cardiol. 2010;56(13):1017-1023.	2
Antman EM, Wiviott SD, Murphy SA, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. Journal of the American College of Cardiology. May 27 2008;51(21):2028-2033.	3
Bath PMW, Cotton D, Martin RH, et al. Effect of combined aspirin and extended-release dipyridamole versus clopidogrel on functional outcome and recurrence in acute, mild ischemic stroke: PRoFESS subgroup analysis. Stroke. Apr 2010;41(4):732-738.	2
Cannon CP, Harrington RA, James S, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet. Jan 23 2010;375(9711):283-293.	3
Chen Y-d, Lu Y-l, Jin Z-n, Yuan F, Lu S-z. A prospective randomized antiplatelet trial of cilostazol versus clopidogrel in patients with bare metal stent. Chinese Medical Journal. Mar 5 2006;119(5):360-366.	3
Diener H-C. The PRoFESS trial: future impact on secondary stroke prevention. Expert Review of Neurotherapeutics. Sep 2007;7(9):1085-1091.	2
Diener H-C, Sacco R, Yusuf S, Steering C, Group PRS. Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS). Cerebrovascular Diseases. 2007;23(5-6):368-380.	2
Diener H-C, Sacco RL, Yusuf S, et al. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study.[see comment][erratum appears in Lancet Neurol. 2008 Nov;7(11):985]. Lancet Neurology. Oct 2008;7(10):875-884.	2
Ge J, Han Y, Jiang H, et al. RACTS: a prospective randomized antiplatelet trial of cilostazol versus ticlopidine in patients undergoing coronary stenting: long-term clinical and angiographic outcome. Journal of Cardiovascular Pharmacology. Aug 2005;46(2):162-166.	3
Ge J, Zhu J, Hong B-K, et al. Prasugrel versus clopidogrel in Asian patients with acute	5

Excluded studies	Exclusion code
coronary syndromes: design and rationale of a multi-dose, pharmacodynamic, phase 3 clinical trial. Current Medical Research & Opinion. Sep 2010;26(9):2077-2085.	
Han Y, Wang S, Li Y, et al. Cilostazol improves long-term outcomes after coronary stent implantation. American Heart Journal. Sep 2005;150(3):568.	3
James S, Akerblom A, Cannon CP, et al. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. American Heart Journal. Apr 2009;157(4):599-605.	3
Kamishirado H, Inoue T, Mizoguchi K, et al. Randomized comparison of cilostazol versus ticlopidine hydrochloride for antiplatelet therapy after coronary stent implantation for prevention of late restenosis. American Heart Journal. Aug 2002;144(2):303-308.	3
Kim SM, Kim DI, Cho HJ, et al. Effects of cilostazol on the drug-eluting stent in native coronary arteries. Korean Circulation Journal. 2007;37(7):304-311.	3
Kozuma K, Hara K, Yamasaki M, et al. Effects of cilostazol on late lumen loss and repeat revascularization after Palmaz-Schatz coronary stent implantation. American Heart Journal. Jan 2001;141(1):124-130.	3
Lee S-W, Park S-W, Hong M-K, et al. Comparison of cilostazol and clopidogrel after successful coronary stenting. American Journal of Cardiology. Apr 1 2005;95(7):859-862.	3
Mariani M, Mariani G, De Servi S. Efficacy and safety of prasugrel compared with clopidogrel in patients with acute coronary syndromes: results of TRITON-TIMI 38 trials. Expert Review of Cardiovascular Therapy. Jan 2009;7(1):17-23.	5
Morrow DA, Wiviott SD, White HD, et al. Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction. Circulation. Jun 2 2009;119(21):2758-2764.	2
Murphy SA, Antman EM, Wiviott SD, et al. Reduction in recurrent cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial. European Heart Journal. Oct 2008;29(20):2473-2479.	5
Nagaoka N, Matsubara T, Okazaki K, Masuda N, Shikaura K, Hotta A. Comparison of ticlopidine and cilostazol for the prevention of restenosis after percutaneous transluminal coronary angioplasty. Japanese Heart Journal. Jan 2001;42(1):43-54.	3
Ochiai M, Eto K, Takeshita S, et al. Impact of cilostazol on clinical and angiographic outcome after primary stenting for acute myocardial infarction. American Journal of Cardiology. A9, 1999 Nov 1 1999;84(9):1074-1076.	3
O'Donoghue M, Antman EM, Braunwald E, et al. The efficacy and safety of prasugrel with and without a glycoprotein IIb/IIIa inhibitor in patients with acute coronary syndromes undergoing percutaneous intervention: a TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) analysis. Journal of the American College of Cardiology. Aug 18 2009;54(8):678-685.	5
Park S-J, Shim WH, Ho DS, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. New England Journal of Medicine. Apr 17 2003;348(16):1537-1545.	3
Park SW, Lee CW, Kim HS, et al. Comparison of cilostazol versus ticlopidine therapy after stent implantation. American Journal of Cardiology. Sep 1 1999;84(5):511-514.	3
Park SW, Lee CW, Kim HS, et al. Effects of cilostazol on angiographic restenosis after coronary stent placement. American Journal of Cardiology. Sep 1	3

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2000;86(5):499-503.	
Pride YB, Tung P, Mohanavelu S, et al. Angiographic and clinical outcomes among patients with acute coronary syndromes presenting with isolated anterior ST-segment depression: a TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) substudy. Jacc: Cardiovascular Interventions. Aug 2010;3(8):806-811.	3
Pride YB, Wiviott SD, Buros JL, et al. Effect of prasugrel versus clopidogrel on outcomes among patients with acute coronary syndrome undergoing percutaneous coronary intervention without stent implantation: a TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel (TRITON)-Thrombolysis in Myocardial Infarction (TIMI) 38 substudy. American Heart Journal. Sep 2009;158(3):e21-26.	5
Sekiguchi M, Hoshizaki H, Adachi H, Ohshima S, Taniguchi K, Kurabayashi M. Effects of antiplatelet agents on subacute thrombosis and restenosis after successful coronary stenting: a randomized comparison of ticlopidine and cilostazol. Circulation Journal. Jul 2004;68(7):610-614.	3
Storey RF, Bliden KP, Patil SB, et al. Incidence of dyspnea and assessment of cardiac and pulmonary function in patients with stable coronary artery disease receiving ticagrelor, clopidogrel, or placebo in the ONSET/OFFSET study. Journal of the American College of Cardiology. Jul 13 2010;56(3):185-193.	3
Take S, Matsutani M, Ueda H, et al. Effect of cilostazol in preventing restenosis after percutaneous transluminal coronary angioplasty. American Journal of Cardiology. Apr 15 1997;79(8):1097-1099.	3
Takeyasu N, Watanabe S, Noguchi Y, Ishikawa K, Fumikura Y, Yamaguchi I. Randomized comparison of cilostazol vs ticlopidine for antiplatelet therapy after coronary stenting. Circulation Journal. Jul 2005;69(7):780-785.	3
Tamura A, Watanabe T, Shinozaki K, Kotoku M, Yano S, Kadota J. Comparison of sarpogrelate and ticlopidine in bare metal coronary stent implantation. International Journal of Cardiology. 2008;126(1):79-83.	3
Tsuchikane E, Takeda Y, Nasu K, Awata N, Kobayashi T. Balloon angioplasty plus cilostazol administration versus primary stenting of small coronary artery disease: final results of COMPASS. Catheterization & Cardiovascular Interventions. Sep 2004;63(1):44-51.	3
Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. New England Journal of Medicine. Sep 10 2009;361(11):1045-1057.	3
Wiviott SD, Antman EM, Gibson CM, et al. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). American Heart Journal. Oct 2006;152(4):627-635.	2
Wiviott SD, Braunwald E, McCabe CH, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial.[see comment]. Lancet. Apr 19 2008;371(9621):1353-1363.	5
Active control trials	
Boehringer Ingelheim P. EARLY 3-months Aggrenox treatment started within 24 hrs of ischemic stroke onset vs after one week 100 mg ASA. ClinicalTrials.gov. 2007.	3
Chairangsarit P, Sithinamsuwan P, Niyasom S, Udommongkol C, Nidhinandana S, Suwantamee J. Comparison between aspirin combined with dipyridamole versus aspirin alone within 48 hours after ischemic stroke event for prevention of recurrent	3

Excluded studies	Exclusion code
stroke and improvement of neurological function: a preliminary study. Journal of the Medical Association of Thailand. Nov 2005;88 Suppl 3:S148-154.	
Chan FKL, Ching JYL, Hung LCT, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding.[see comment]. New England Journal of Medicine. Jan 20 2005;352(3):238-244.	3
Dalainas I, Nano G, Bianchi P, Stegher S, Malacrida G, Tealdi DG. Dual antiplatelet regime versus acetyl-acetic acid for carotid artery stenting. Cardiovascular & Interventional Radiology. Jul-Aug 2006;29(4):519-521.	4
Diener H-C, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial.[see comment]. Lancet. Jul 24-30 2004;364(9431):331-337.	6
Huang Y, Cheng Y, Wu J, et al. Cilostazol as an alternative to aspirin after ischaemic stroke: a randomised, double-blind, pilot study.[Erratum appears in Lancet Neurol. 2008 Aug;7(8):675]. Lancet Neurology. Jun 2008;7(6):494-499.	3
Kunishima T, Musha H, Eto F, et al. A randomized trial of aspirin versus cilostazol therapy after successful coronary stent implantation. Clinical Therapeutics. Sep-Oct 1997;19(5):1058-1066.	3
Lai K, Chu K, Hui W, al. e. Esomeprazole with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. Clin Gastroenterol Hepatol. 2006;4:860-865.	3
Mehta SR, Bassand J-P, Chrolavicius S, et al. Design and rationale of CURRENT-OASIS 7: a randomized, 2 x 2 factorial trial evaluating optimal dosing strategies for clopidogrel and aspirin in patients with ST and non-ST-elevation acute coronary syndromes managed with an early invasive strategy. American Heart Journal. Dec 2008;156(6):1080-1088.e1081.	3
Tsuchikane E, Fukuhara A, Kobayashi T, et al. Impact of cilostazol on restenosis after percutaneous coronary balloon angioplasty. Circulation. Jul 6 1999;100(1):21-26.	3
Yoon Y, Shim WH, Lee DH, et al. Usefulness of cilostazol versus ticlopidine in coronary artery stenting. American Journal of Cardiology. Dec 15 1999;84(12):1375-1380.	3
Placebo controlled trials	
Aronow HD, Steinhubl SR, Brennan DM, Berger PB, Topol EJ, Investigators C. Bleeding risk associated with 1 year of dual antiplatelet therapy after percutaneous coronary intervention: Insights from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. American Heart Journal. Feb 2009;157(2):369-374.	5
Bartorelli AL, Tamburino C, Trabattoni D, et al. Comparison of two antiplatelet regimens (aspirin alone versus aspirin + ticlopidine or clopidogrel) after intracoronary implantation of a carbofilm-coated stent. American Journal of Cardiology. Apr 15 2007;99(8):1062-1066.	3
Becker RC, Moliterno DJ, Jennings LK, et al. Safety and tolerability of SCH 530348 in patients undergoing non-urgent percutaneous coronary intervention: a randomised, double-blind, placebo-controlled phase II study.[see comment]. Lancet. Mar 14 2009;373(9667):919-928.	3
Berger JS, Bhatt DL, Steinhubl SR, et al. Smoking, clopidogrel, and mortality in patients with established cardiovascular disease. Circulation. Dec 8 2009;120(23):2337-2344.	4
Berger PB, Bhatt DL, Fuster V, et al. Bleeding complications with dual antiplatelet therapy among patients with stable vascular disease or risk factors for vascular disease: results from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. Circulation. Jun 15 2010;121(23):2575-2583.	6

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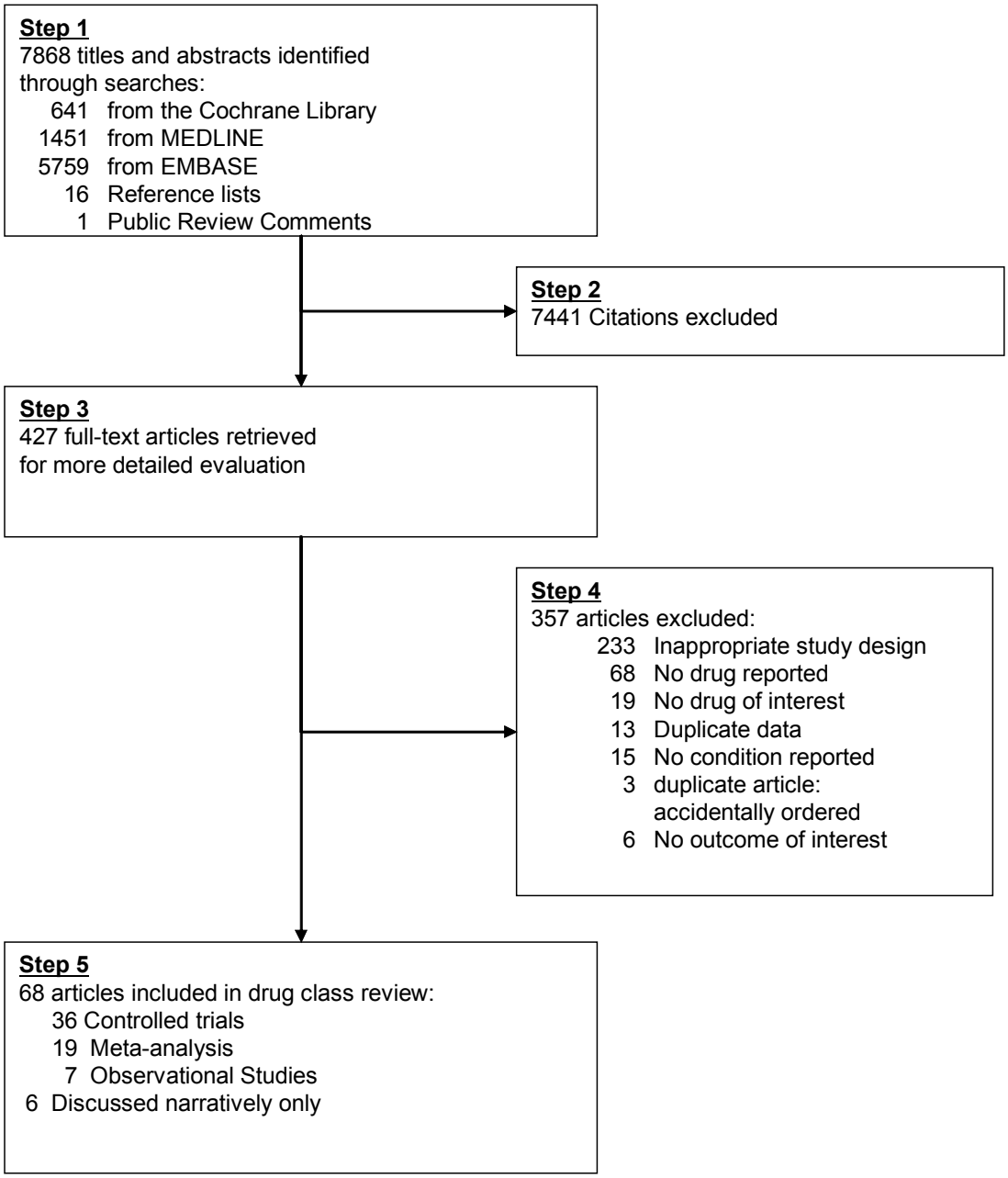
Best PJM, Steinhubl SR, Berger PB, et al. The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: results from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. American Heart Journal. Apr 2008;155(4):687-693.	2
Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. New England Journal of Medicine. Nov 11 2010;363(20):1909-1917.	3
Bhatt DL, Flather MD, Hacke W, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial.[see comment]. Journal of the American College of Cardiology. May 15 2007;49(19):1982-1988.	6
Brener SJ, Steinhubl SR, Berger PB, Brennan DM, Topol EJ, for the CI. Prolonged dual antiplatelet therapy after percutaneous coronary intervention reduces ischemic events without affecting the need for repeat revascularization: insights from the CREDO trial. Journal of Invasive Cardiology. Jul 2007;19(7):287-290.	5
Byrne RA, Schulz S, Mehilli J, et al. Rationale and design of a randomized, double-blind, placebo-controlled trial of 6 versus 12 months clopidogrel therapy after implantation of a drug-eluting stent: The Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) study. American Heart Journal. Apr 2009;157(4):620-624.e622.	2
Collet J-P, Montalescot G, Steg PG, et al. Clinical outcomes according to permanent discontinuation of clopidogrel or placebo in the CHARISMA trial. Archives of cardiovascular diseases. Jun-Jul 2009;102(6-7):485-496.	5
Desai NR, Mega JL, Jiang S, Cannon CP, Sabatine MS. Interaction between cigarette smoking and clinical benefit of clopidogrel. Journal of the American College of Cardiology. Apr 14 2009;53(15):1273-1278.	3
Diener HC. Aspirin and clopidogrel after recent ischemic stroke or transient ischemic attack. Cardiology Review. 2006;23(2):37-41.	3
Douglas JS, Jr., Holmes DR, Jr., Kereiakes DJ, et al. Coronary stent restenosis in patients treated with cilostazol. Circulation. Nov 1 2005;112(18):2826-2832.	3
Douglas JS, Weintraub WS, Holmes D. Rationale and design of the randomized, multicenter, cilostazol for RESTenosis (CREST) trial. Clinical Cardiology. Oct 2003;26(10):451-454.	2
Goto S, Yamaguchi T, Ikeda Y, Kato K, Yamaguchi H, Jensen P. Safety and exploratory efficacy of the novel thrombin receptor (PAR-1) antagonist SCH530348 for non-ST-segment elevation acute coronary syndrome. Journal of Atherosclerosis & Thrombosis. Feb 26 2010;17(2):156-164.	3
Gotoh F, Ohashi Y, Tohgi H, et al. Design and organization of the Cilostazol Stroke Prevention Study. Journal of Stroke & Cerebrovascular Diseases. 2000;9(1):36-44.	3
Gotoh F, Tohgi H, Hirai S, et al. Cilostazol stroke prevention study: A placebo-controlled double-blind trial for secondary prevention of cerebral infarction. Journal of Stroke & Cerebrovascular Diseases. 2000;9(4):147-157.	3
Hankey GJ, Hacke W, Easton JD, et al. Effect of clopidogrel on the rate and functional severity of stroke among high vascular risk patients: a prespecified substudy of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial. Stroke. Aug 2010;41(8):1679-1683.	2
Hart RG, Bhatt DL, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of stroke in patients with a history of atrial fibrillation: subgroup analysis of the CHARISMA randomized trial. Cerebrovascular Diseases. 2008;25(4):344-347.	4
Hiatt WR, Money SR, Brass EP. Long-term safety of cilostazol in patients with peripheral artery disease: the CASTLE study (Cilostazol: A Study in Long-term Effects). Journal of Vascular Surgery. Feb 2008;47(2):330-336.	3
Kelly RV, Hsu A, Topol E, Steinhubl S. The influence of body mass index on	5

Excluded studies	Exclusion code
outcomes and the benefit of antiplatelet therapy following percutaneous coronary intervention. Journal of Invasive Cardiology. Mar 2006;18(3):115-119.	
Keltai M, Tonelli M, Mann JFE, et al. Renal function and outcomes in acute coronary syndrome: impact of clopidogrel. European Journal of Cardiovascular Prevention & Rehabilitation. Apr 2007;14(2):312-318.	5
Kwon SU, Cho Y-J, Koo J-S, et al. Cilostazol prevents the progression of the symptomatic intracranial arterial stenosis: the multicenter double-blind placebo-controlled trial of cilostazol in symptomatic intracranial arterial stenosis. Stroke. Apr 2005;36(4):782-786.	3
Lee S-W, Chun K-J, Park S-W, et al. Comparison of Triple antiplatelet therapy and dual antiplatelet therapy in patients at high risk of restenosis after drug-eluting stent implantation (from the DECLARE-DIABETES and -LONG Trials). American Journal of Cardiology. Jan 15 2010;105(2):168-173.	3
Lee S-W, Park S-W, Kim Y-H, et al. Drug-eluting stenting followed by cilostazol treatment reduces late restenosis in patients with diabetes mellitus the DECLARE-DIABETES Trial (A Randomized Comparison of Triple Antiplatelet Therapy with Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Diabetic Patients). Journal of the American College of Cardiology. Mar 25 2008;51(12):1181-1187.	3
Lee S-W, Park S-W, Kim Y-H, et al. Comparison of triple versus dual antiplatelet therapy after drug-eluting stent implantation (from the DECLARE-Long trial). American Journal of Cardiology. Oct 1 2007;100(7):1103-1108.	3
Mak K-H, Bhatt DL, Shao M, et al. The influence of body mass index on mortality and bleeding among patients with or at high-risk of atherothrombotic disease. European Heart Journal. Apr 2009;30(7):857-865.	4
Min P-K, Jung J-H, Ko Y-G, Choi D, Jang Y, Shim W-H. Effect of cilostazol on in-stent neointimal hyperplasia after coronary artery stenting: a quantative coronary angiography and volumetric intravascular ultrasound study. Circulation Journal. Nov 2007;71(11):1685-1690.	3
Price MJ, Berger PB, Angiolillo DJ, et al. Evaluation of individualized clopidogrel therapy after drug-eluting stent implantation in patients with high residual platelet reactivity: design and rationale of the GRAVITAS trial. American Heart Journal. 2009 May 2009;157(5):818-824.	3
Saw J, Brennan DM, Steinhubl SR, et al. Lack of evidence of a clopidogrel-statin interaction in the CHARISMA trial.[see comment]. Journal of the American College of Cardiology. Jul 24 2007;50(4):291-295.	5
Soga Y, Yokoi H, Kawasaki T, et al. Efficacy of cilostazol after endovascular therapy for femoropopliteal artery disease in patients with intermittent claudication. Journal of the American College of Cardiology. Jan 6 2009;53(1):48-53.	3
Testai FD, Cursio JF, Gorelick PB. Effect of sex on outcome after recurrent stroke in African Americans: results from the African American Antiplatelet Stroke Prevention Study. Journal of Stroke & Cerebrovascular Diseases. Jul-Aug 2010;19(4):321-325.	3
Wang TH, Bhatt DL, Fox KAA, et al. An analysis of mortality rates with dual-antiplatelet therapy in the primary prevention population of the CHARISMA trial.[see comment]. European Heart Journal. Sep 2007;28(18):2200-2207.	6
Wong KSL, Chen C, Fu J, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. Lancet Neurology. May 2010;9(5):489-497.	2

Appendix E. Results of literature search from Original Report and Update 1



Appendix F. Strength of evidence

Table 1: Acute coronary syndrome: Clopidogrel/aspirin compared with placebo/aspirin (CURE – 12 months)

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**RR (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
1/N= 12562	Low (RCT/Good)	Consistent	Indirect	Precise	0.93 (0.81 to 1.07)[a]	Moderate
Cardiovascular mortality						
1/N= 12562	Low (RCT/Good)	Consistent	Indirect	Precise	0.93 (0.80 to 1.10)	Moderate
MI						
1/N= 12562	Low (RCT/Good)	Consistent	Indirect	Precise	0.78 (0.68 to 0.90)	Moderate
Major bleeding						
1/N= 12562	Low (RCT/Good)	Consistent	Indirect	Imprecise	1.37 (1.13 to 1.67)[a]	Moderate
Withdrawal due to adverse events						
1/N= 12562					NR	Insufficient

[a] Calculated by OR EPC using StatsDirect.

Table 2: Acute coronary syndrome: clopidogrel compared with aspirin (CAPRIE MI subgroup – 1-3 years [mean 1.9 years])

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**RR (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
					NR by subgroup	Insufficient
Cardiovascular mortality[c]						
1/N= 6302	Low (RCT/Good)	Unknown	Indirect	Imprecise	1.16 (0.88 to 1.51)[a,b]	Low
MI – nonfatal [c]						
1/N= 6302	Low (RCT/Good)	Unknown	Indirect	Imprecise	0.95 (0.76 to 1.19) [a,b]	Low
Major bleeding						
					NR by subgroup	Insufficient
Withdrawal due to adverse events						
					NR by subgroup	Insufficient

[a] Calculated by OR EPC using StatsDirect.
[b] Patient years at risk.
[c] Calculated from data reported in CAPRIE Table 7.

Table 3: Acute coronary syndrome: Clopidogrel/aspirin compared with placebo/aspirin (CHARISMA symptomatic subgroup – median 28 months)

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**RR (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
					NR by subgroup	Insufficient
Cardiovascular mortality						
1/N= 12153	Low (RCT/Good)	Consistent	Indirect	Imprecise	No significant effect on cardiovascular death in the symptomatic subgroup.	Low
MI – nonfatal						
					NR by subgroup	Insufficient
Major bleeding						
1/N= 12153	Low (RCT/Good)	Consistent	Indirect	Imprecise	C: 1.6 % P: 1.4 %	Low
Withdrawal due to adverse events						
					NR by subgroup	Insufficient

[a] Calculated by OR EPC using StatsDirect; *patient years at risk

Table 4: Coronary revascularization: Prasugrel compared with clopidogrel (TRITON-TIMI 38[1], JUMBO-TIMI 26[2], PRINCIPLE-TIMI 44[3])

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Hazard ratio (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
1/N=13608[1]	Low (RCT/Good)	Unknown	Direct	Precise	0.95 (0.78 to 1.16)	High
2/N=1106[2,3]	Low (RCT/Fair)	Unknown	Direct	Imprecise	3 prasugrel, 0 clopidogrel	Low
Cardiovascular mortality						
1/N=13608[1] 2/N=1106[2,3]	Low (RCT/Good)	Unknown	Direct	Imprecise	0.89 (0.70 to 1.12) NR	Moderate Insufficient
Revascularization						
1/N=13608[1]	Low (RCT/Good)	Unknown	Direct	Precise	0.67 (0.55 to 0.82)[a]	High
2/N=1106[2,3]	Low (RCT/Fair)	Unknown	Direct	Imprecise	4 prasugrel, 7 clopidogrel	Low
Major bleeding (TIMI, non-CABG related)						
1/N=13608[1]	Low (RCT/Good)	Unknown	Direct	Imprecise	1.32 (1.03 to 1.68)	Moderate
2/N=1106[2,3]	Low (RCT/Fair)	Unknown	Direct	Imprecise	11 prasugrel, 3 clopidogrel	Low
Withdrawal due to adverse events						
1/N=13608[1] 2/N=1106[2,3]	Low (RCT/Good)	Unknown	Direct	Imprecise	1.14 (1.00 to 1.29) NR	Moderate Insufficient

[a] Calculated by OR EPC using StatsDirect

Table 5: Coronary revascularization: Ticlopidine/aspirin compared with clopidogrel/aspirin (CLASSICS – 28 days)

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**RR (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
1/N=675 (2 arms)	Low (RCT/Good)				NR	Insufficient
Cardiovascular mortality						
1/N=675 (2 arms)	Low (RCT/Good)	Consistent	Direct	Imprecise	No events	Insufficient
Revascularization						
1/N=675 (2 arms)	Low (RCT/Good)	Consistent	Direct	Imprecise	0.99(0.06-15.69)[a]	Moderate
Major bleeding						
1/N=675 (2 arms)	Low (RCT/Good)	Consistent	Direct	Imprecise	0.99 (0.27-3.57)[a]	Moderate
Withdrawal due to adverse events						
1/N=675 (2 arms)	Low (RCT/Good)	N/A	Direct	Imprecise	1.62(0.91-2.89)[a]	Low

[a] Calculated by OR EPC using StatsDirect

Table 6: Coronary revascularization: Ticlopidine/aspirin compared with clopidogrel/aspirin (Di Pasquale 2005 – 6 months)

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**RR (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
1/N=428	Med (RCT/Fair)				NR	Insufficient
Cardiovascular mortality						
1/N=428	Med (RCT/Fair)				NR	Insufficient
Revascularization						
1/N=428	Med (RCT/Fair)	Consistent	Direct	Imprecise	0.91 (0.62-1.33)[a]	Low
Major bleeding						
1/N=428	Med (RCT/Fair)	Consistent	Direct	Imprecise	1 (0.178-5.63)[a]	Low
Withdrawal due to adverse events						
1/N=428	Med (RCT/Fair)				NR	Insufficient

[a] Calculated by OR EPC using StatsDirect

Table 7: Coronary revascularization: Ticlopidine/aspirin compared with clopidogrel/aspirin (Mueller 2003 – 4-week treatment period, 28-month event rates)

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**RR (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
1/N=700	Med (RCT/Fair)	NA	Direct	Precise	0.32 (0.15-0.66)[a]	Low
Cardiovascular mortality						
1/N=700	Med (RCT/Fair)	Inconsistent	Direct	Precise	0.32 (0.15-0.69)[a]	Low
Revascularization						
1/N=700	Med (RCT/Fair)				NR	Insufficient
Major bleeding						
1/N=700	Med (RCT/Fair)				NR	Insufficient
Withdrawal due to adverse events						
1/N=700	Med (RCT/Fair)				NR	Insufficient

[a] Calculated by OR EPC using StatsDirect.

Table 8: Coronary revascularization: Ticlopidine/aspirin compared with clopidogrel/aspirin (Mueller 2000 – 30 days)

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**RR (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
1/N=700	Med (RCT/Fair)				NR	Insufficient
Cardiovascular mortality						
1/N=700	Med (RCT/Fair)	Inconsistent	Direct	Imprecise	1.03(0.06-16.39)[a]	Low
Revascularization						
1/N=700	Med (RCT/Fair)	Consistent	Direct	Imprecise	0.34 (0.07-1.69)[a]	Low
Major bleeding						
1/N=700	Med (RCT/Fair)				NR	Insufficient
Withdrawal due to adverse events						
1/N=700	Med (RCT/Fair)				NR	Insufficient

[a] Calculated by OR EPC using StatsDirect.

Table 9: Coronary revascularization: Ticlopidine/aspirin compared with clopidogrel/aspirin (Taniuchi 2001 – 2-week treatment period, 30-day event rates)

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of Studies; number of Subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**RR (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
1/N=1016	Med (RCT/Fair)				NR	Insufficient
Cardiovascular mortality						
1/N=1016	Med (RCT/Fair)	Inconsistent	Direct	Imprecise	2.52 (0.67-9.46)[a]	Low
Revascularization						
1/N=1016	Med (RCT/Fair)	Consistent	Direct	Imprecise	0.95 (0.43-2.09)[a]	Low
Major bleeding						
1/N=1016	Med (RCT/Fair)				NR	Insufficient
Withdrawal due to adverse events						
1/N=1016	Med (RCT/Fair)				NR	Insufficient

[a] Calculated by OR EPC using StatsDirect.

Table 10: Stroke or transient ischemic attack: Extended-release dipyridamole plus aspirin compared with clopidogrel plus aspirin (PRoFESS trial)

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
1/N=20,332	Low (RCT/Good)	NA	Direct	Precise	HR 0.97 (0.87 to 1.07)	High
Cardiovascular mortality						
1/N=20,332	Low (RCT/Good)	NA	Direct	Precise	HR 0.94 (0.82 to 1.07)	High
Recurrent stroke						
1/N=20,332	Low (RCT/Good)	NA	Direct	Precise	HR 1.01 (0.92 to 1.11)	High
Major bleeding						
1/N=20,332	Low (RCT/Good)	NA	Direct	Imprecise	HR 1.15 (1.00 to 1.32)	Moderate
Withdrawal due to adverse events						
1/N=20,332	Low (RCT/Good)	NA	Direct	Precise	RR 1.54 (1.43 to 1.66)[a]	High

[a] Calculated by OR EPC using StatsDirect.

Table 11: Stroke or transient ischemic attack: Clopidogrel plus aspirin compared with ticlopidine plus aspirin

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality ("considered to be related to study medication")						
2; N=1869	RCT/Fair	Consistent	Direct	Imprecise	RR 0.99 (0.17 to 5.58)[a]	Moderate
Cardiovascular mortality						
2; N=1862	RCT/Fair	Consistent	Direct	Imprecise	No events	Moderate
Cerebral infarction						
2; N=1862	RCT/Fair	Consistent	Direct	Imprecise	HR 0.92 (0.52 to 1.63)	Moderate
Major bleeding						
2; N=1869	RCT/Fair	Consistent	Direct	Imprecise	RR 1.53 (0.68 to 3.45)[a,b]	Moderate
Neutropenia						
2; N=1869	RCT/Fair	Consistent	Direct	Precise	RR 0.32 (0.15 to 0.65)[a,b]	Moderate
Withdrawal due to adverse events						
2; N=1869	RCT/Fair	Unclear[c]	Direct	Precise	RR 0.71 (0.58 to 0.87)[a]	Moderate

[a] Relative risks calculated by OR EPC using StatsDirect.
[b] Frequencies estimated from Figure 3 in Uchiyama 2009.
[c] Separate frequencies for the IIIa and IIIb studies are not available from either the Fukuuchi 2008 or Uchiyama 2009 publications.

Table 12: Stroke or transient ischemic attack: Fixed combination of extended-release dipyridamole compared with aspirin alone

Domains pertaining to strength of evidence					Magnitude of effect[a]	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
2; N=6038	Medium (RCT; Fair)	Consistent	Indirect	Precise	RR 0.96 (0.83 to 1.13)	Moderate
Cardiovascular mortality						
1; N=2739	Medium (RCT; Fair	NA	Indirect	Imprecise	RR 0.74 (0.51 to 1.08)	Moderate
Cerebral infarction						
3; N=7329	Medium (RCT; Fair)	Inconsistent	Indirect	Precise	RR 0.84 (0.73 to 0.98)	Moderate
Major bleeding						
2; N=6038	Medium (RCT; Fair)	Inconsistent	Indirect	Imprecise	RR 0.85 (0.61 to 1.19)	Low
Withdrawal due to adverse events[b]						
1;N=1294 (JASAP, duration=1 year)	Medium (RCT; Fair)	NA	Indirect	Imprecise	RR 1.10 (0.86 to 1.39)	Low
1;N=3299 (ESPS-2, duration=2 years)	Medium (RCT; Fair)	NA	Indirect	Precise	RR 1.86 (1.53 to 2.25)	Moderate
1;N=2763 (ESPRIT, duration=3.5 years)	Medium (RCT; Fair)	NA	Indirect	Precise	RR 7.35 (5.22 to 10.38)	Moderate

[a] Relative risks calculated by OR EPC using StatsDirect.
[b] Pooled relative risk is not presented due to significant statistical heterogeneity, possibly due to the pattern of increased magnitude of risk of withdrawal over time with the combination of extended-release dipyridamole plus aspirin.

Table 13: Stroke or transient ischemic attack: Clopidogrel compared with aspirin alone

Domains pertaining to strength of evidence					Magnitude of effect[a]	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality: Not reported						
Cardiovascular mortality (fatal stroke, fatal MI, other vascular deaths)						
1; N=6,451	Medium (RCT; Fair)	NA	Indirect	Precise	RR 0.99 (0.75 to 1.29)	Moderate
Stroke (fatal and nonfatal)						
1; N=6,451	Medium (RCT; Fair)	NA	Indirect	Precise	RR 0.92 (0.79 to 1.07)	Moderate
Major bleeding: Not reported						
Withdrawal due to adverse events: Not reported						

[a] Relative risks calculated by OR EPC using StatsDirect.

Table 14: Stroke or transient ischemic attack: Clopidogrel plus aspirin compared with aspirin alone (FASTER trial)

Domains pertaining to strength of evidence					Magnitude of effect[a]	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality: Not reported						
Cardiovascular mortality: Not reported						
Stroke, fatal and nonfatal[a]						
1; N=193	Moderate (RCT; Fair)	NA	Indirect	Imprecise	RR 0.5 (0.2 to 1.5)	Low
Major bleeding: Not reported						
Severe extracranial hemorrhage						
1; N=392	Moderate (RCT; Fair)	NA	Indirect	Imprecise	RD 0.5% (-0.5 to 1.5)	Low
Withdrawal due to adverse events: Not reported						

[a] For effectiveness outcomes, we focused only on the comparison of clopidogrel to placebo in the groups who were not receiving simvastatin.
[b] For bleeding outcomes, we evaluated the comparison of clopidogrel to no clopidogrel, which included patients taking concomitant simvastatin.

Table 15: Stroke or transient ischemic attack: Ticlopidine compared with aspirin alone

Domains pertaining to strength of evidence					Magnitude of effect[a]	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
2; N=4878	Medium (RCT; Fair)	Consistent	Indirect	Precise	RR 0.94 (0.79 to 1.12)	Moderate
Cardiovascular mortality						
2; N=4878	Medium (RCT; Fair)	Consistent	Indirect	Imprecise	RR 1.16 (0.89 to 1.52)	Moderate
Stroke, fatal and nonfatal						
2; N=4878	Medium (RCT; Fair)	Consistent	Indirect	Precise	RR 0.94 (0.81 to 1.10)	Moderate
Major bleeding: Not reported						
GI bleeding						
2; N=4854	Medium (RCT; Fair)	Consistent	Indirect	Precise	RR 0.38 (0.19 to 0.76)	Moderate
Neutropenia						
2; N=4854	Medium (RCT; Fair)	Consistent	Indirect	Precise	RR 2.18 (1.30 to 3.66)	Moderate
Withdrawal due to adverse events						
2; N=4854	Medium (RCT; Fair)	Consistent	Indirect	Precise	RR 1.37 (1.19 to 1.57)	Moderate

[a] Relative risks calculated by OR EPC using StatsDirect.

Table 16: Peripheral vascular disease: Clopidogrel compared with aspirin (PAD subgroup from CAPRIE)

Domains pertaining to strength of evidence					Magnitude of effect[a]	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% confidence interval)**	**High, moderate, low, insufficient**
Cardiovascular mortality (fatal stroke, fatal MI, other vascular death from Table 7 of 1996 Lancet publication)						
1/N=11592	Low (RCT/Good)	NA	Indirect	Imprecise	RR 0.78 (0.60 to 1.01)	Moderate
All-cause mortality, revascularization, major bleeding, withdrawals due to adverse events not reported for PAD subgroup						

[a] Relative risks calculated by OR EPC using StatsDirect.

Table 17: Peripheral vascular disease: Clopidogrel plus aspirin compared with aspirin alone (CASPAR trial)

Domains pertaining to strength of evidence					Magnitude of effect[a]	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
1/N=851	Moderate (RCT/Fair)	NA	Indirect	Imprecise	HR 1.44 (0.77 to 2.68)	Low
Cardiovascular mortality						
1/N=851	Moderate (RCT/Fair)	NA	Indirect	Imprecise	HR 1.49 (0.73 to 3.01)	Low
Revascularization						
1/N=851	Moderate (RCT/Fair)	NA	Indirect	Imprecise	HR 0.89 (0.65 to 1.23)	Low
Major bleeding (“severe”)						
1/N=848	Moderate (RCT/Fair)	NA	Indirect	Imprecise	RR 1.78 (0.63 to 5.04)[a]	Low
Withdrawal due to adverse events – not reported						

[a] Relative risks calculated by OR EPC using StatsDirect.

Table 18: Key Question 3 – therapy duration: Clopidogrel vs. placebo: 30-days vs. 12 months (PCI-CURE)

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**RR (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
1/N=2658	Low (RCT/Good)				NR	Insufficient
Cardiovascular mortality						
1/N=2658	Low (RCT/Good)	Consistent	Indirect	Imprecise	1.07 (0.65 to 1.75)	Low
Revascularization						
1/N=2658	Low (RCT/Good)	Consistent	Indirect	Imprecise	0.82 (0.68 to 1.00)	Moderate
Major bleeding						
1/N=2658	Low (RCT/Good)	Consistent	Indirect	Imprecise	1.12 (0.70 to 1.78)	Low
Withdrawal due to adverse events						
1/N=2658	Low (RCT/Good)				NR	Insufficient

[a] Calculated by OR EPC using StatsDirect.

Table 19: Key Question 3 – therapy duration: Clopidogrel vs. placebo: 28-days vs. 12 months (CREDO)

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**RR (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
1/N=2116	Low (RCT/Good)	Consistent	Indirect	Imprecise	0.76 (0.58 to 1.00)[a]	Moderate
Cardiovascular mortality						
1/N=2116	Low (RCT/Good)				NR	Insufficient
Revascularization						
1/N=2116	Low (RCT/Good)	Consistent	Indirect	Imprecise	1.01 (0.86 to 1.20)[a]	Low
Major bleeding						
1/N=2116	Low (RCT/Good)	Consistent	Indirect	Imprecise	1.32 (0.98 to 1.78)[a]	Moderate
Withdrawal due to adverse events						
1/N=2116	Low (RCT/Good)				NR	Insufficient

[a] Calculated by OR EPC using StatsDirect.

Table 20: Key Question 3 – therapy duration: Pooled analysis of clopidogrel vs. placebo: 1 month vs. 6 months (Akbulut 2004[1] n=78, Pekdemier 2003[2] n=278, Bernardi 2007[3] n=921)

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**RR (95% confidence interval)**	**High, moderate, low, insufficient**
All-cause mortality						
2/N=1199[2,3]	Low (RCT/Fair)	Consistent	Indirect	Imprecise	0.86 (0.40 to 1.84)[a]	Low
Cardiovascular mortality						
2/N=999[1,3]	Low (RCT/Fair)	Inconsistent	Indirect	Imprecise	0.50 (0.15 to 1.65)[a]	Low
Revascularization						
3/N=1277[1,2,3]	Low (RCT/Fair)	Consistent	Indirect	Precise	0.65 (0.43 to 0.97)[a]	Moderate
Major bleeding						
3/N=1277[1,2,3]	Low (RCT/Fair)	Inconsistent	Indirect	Imprecise	1.10 (0.44 to 2.30)[a]	Low
Withdrawal due to adverse events						
1/N=921[3]	Low (RCT/Fair)	NA	Indirect	Imprecise	2.20 (0.81 to 6.04)[a]	Low

[a] Calculated by OR EPC using StatsDirect.