Drug Class Review
on
Newer Antiplatelet Agents

Final Report Update 1

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Original Report Date: November 2005
A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. 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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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date. Prior version of this report can be accessed at the DERP website.

TABLE OF CONTENTS

EVIDENCE TABLES – Published in a separate document

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INTRODUCTION

I. Scope of the problem

Atherosclerosis often starts in late adolescence or early adulthood, although clinical manifestations typically occur years later. Statistics from 2003 indicate that approximately 71.3 million Americans have at least one type of cardiovascular disease (CVD) including ischemic coronary heart disease, stroke, and/or peripheral arterial disease (PAD). An estimated 2,500 Americans die of CVD each day, an average of 1 death every 35 seconds. About 700,000 people will experience a new or recurrent stroke each year, meaning that on average, every 45 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 elevated myocardial infarction (NSTEMI) or even a ST-segment elevated MI (STEMI). All of these presentations except stable angina are often referred to as acute coronary syndrome (ACS). 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 manifests 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 MI, recurrent angina or progression to severe angina and nonfatal stroke. In the meta-analysis included in the 2002 Antithrombotic Trialists Collaboration,[2] aspirin was found to prevent vascular death by approximately 15% and nonfatal vascular events by about 30%. Many clinical practice guidelines for the use of antiplatelet agents have included aspirin as the primary oral antiplatelet agent for acute vascular events. For example, the American College of Cardiology (ACC)/American Heart Association[3] (AHA) recommends that aspirin should be administered as soon as possible after presentation and continued indefinitely (Level of Evidence: A) for the treatment of unstable angina (UA) and NSTEMI (ACS). The Seventh American College of Chest Physicians[4] (ACCP) Conference on Antithrombotic and Thrombolytic Therapy recommends for ACS, aspirin should be given at initial doses of 160 mg to 325 mg and then indefinitely at 75 to 162 mg daily (Grade 1A).

In the past decade, newer antiplatelet agents have begun to come to the forefront as adjuncts to or substitutes for aspirin in certain clinical situations. However, their role is evolving and it is not always clear how best to utilize these drugs. The following review evaluates these newer antiplatelet agents including aspirin (ASA) 25 mg /extended-release dipyridamole 200 mg (Aggrenox®), and the thienopyridines; clopidogrel (Plavix®) and ticlopidine (Ticlid®). A comparison of the agents in the context of secondary prevention of specific vascular disease is included.

Recent evidence regarding the long-term use of clopidogrel in patients who have received a drug-eluting stent was not available at the time this update was conducted (JAMA, Published online December 5, 2006, www.jama.com) This evidence will be included in future updates of this review.

II. Summary of Recommendations

The newer antiplatelet agents have already been incorporated into various clinical practice guidelines and disease specific recommendations. The following outlines a few of these recommendations:

A. 2002 Update to the Guidelines from the American College of Cardiology (ACC)/American Heart Association[3] (AHA) recommends the following as Class I recommendations for the treatment of unstable angina (UA) and NSTEMI (ACS). (Appendix A describes the ACC/AHA method of grading evidence.)

1. Clopidogrel should be administered to hospitalized patients who are unable to take ASA because of hypersensitivity or major GI intolerance. (Level of Evidence: A)
2. In hospitalized patients in whom an early nonintervention approach is planned, clopidogrel should be added to aspirin as soon as possible on admission and administered for at least 1 month (Level of Evidence: A) and for up to 9 months. (Level of Evidence: B)
3. In patients for whom a percutaneous coronary intervention (PCI) is planned and who are not at high risk for bleeding, clopidogrel should be started and continued for at least 1 month (Level of Evidence: A) and up to 9 months. (Level of Evidence: B)
4. In patients taking clopidogrel in whom elective coronary artery bypass grafting (CABG) is planned, the drug should be withheld for 5 to 7 days. (Level of Evidence: B)

B. The European Society of Cardiology[5] recommends the following for ACS:

1. Clopidogrel in addition to standard therapy, including aspirin, should be administered for at least 9–12 months. (Level of Evidence: B)
2. Clopidogrel may also be recommended for immediate and long-term therapy in patients who do not tolerate aspirin and is recommended for patients receiving a stent. (Level of Evidence: B)

C. The Seventh American College of Chest Physicians (ACCP)[4 6 7]recommends the following: (Appendix A describes the ACCP method of grading evidence.)

1. Patients with stable chronic coronary disease and a risk profile indicating a high likelihood of developing AMI should receive long-term therapy with clopidogrel in addition to ASA (Grade 2C).
2. For all NSTE ACS patients with an aspirin allergy, immediate treatment with clopidogrel, 300 mg bolus oral, followed by 75 mg daily indefinitely (Grade 1A).
3. A combination of aspirin and ticlopidine or aspirin and clopidogrel is preferred over systemic anticoagulation therapy following stent placement (Grade 1A).
4. Clopidogrel is preferred over ticlopidine following stent placement (Grade 1A).

5. A loading dose of 300 mg of clopidogrel should be given at least 6 hours prior to a planned percutaneous coronary intervention (PCI) (Grade 1B). If clopidogrel is started less than 6 hours prior to a planned PCI, a 600 mg loading dose of clopidogrel is suggested (Grade 2C).
6. For PCI patients who cannot tolerate aspirin, clopidogrel 300 mg or ticlopidine 500 mg may be administered at least 24 hours prior to planned PCI. (Grade 2C)
7. In all NSTE ACS patients in whom diagnostic catherization will be delayed or when coronary bypass surgery will not occur until >5 days following coronary angiography, administer clopidogrel immediately as bolus therapy (300 mg), followed by 75 mg/d for 9-12 months in addition to aspirin (Grade 1A).
8. For chronic limb ischemia, clopidogrel rather than ticlopidine should be used (Grade 1C+); aspirin should be used instead of clopidogrel (Grade 2A).
9. In noncardioembolic stroke or transient ischemic attack (TIA), a combination of ASA and extended release dipyridamole (ERDP) twice a day is preferred over aspirin (Grade 2A); clopidogrel is also preferred over aspirin (Grade 2B).
10. In patients who have experienced a noncardioembolic stroke or TIA (i.e., atherothrombotic, lacunar, or cryptogenic), an antiplatelet agent is recommended (Grade 1A). Aspirin at a dose of 50 to 325 mg every day; the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice a day; or clopidogrel 75 mg every day are all acceptable options for initial therapy.
11. In patients who have experienced a noncardioembolic stroke or TIA, use of the combination of aspirin and extended-release dipyridamole 25/200 mg twice a day over aspirin (Grade 2A), and clopidogrel over aspirin (Grade 2B) is suggested.

D. 2005 Guideline Update for Percutaneous Coronary Intervention from American College of Cardiology (ACC) and American Heart Association (AHA)[8]

1. Patients already taking daily chronic aspirin therapy should take 75 to 325 mg of aspirin before the PCI procedure is performed. (Level of Evidence: A)
2. Patients not already taking daily chronic aspirin therapy should be given 300 to 325 mg of aspirin at least 2 hours and preferably 24 hours before the PCI procedure is performed. (Level of Evidence: C)
3. After the PCI procedure, in patients with neither aspirin resistance, allergy, nor increased risk of bleeding, aspirin 325 mg daily should be given for at least 1 month after bare-metal stent implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which daily chronic aspirin use should be continued indefinitely at a dose of 75 to 162 mg. (Level of Evidence: B)
4. A loading dose of clopidogrel should be administered before PCI is performed. (Level of Evidence: A) An oral loading dose of 300 mg, administered at least 6 hours before the procedure has the best established evidence of efficacy. (Level of Evidence: B)
5. For patients with an absolute contraindication to aspirin, it is reasonable to give a 300 mg loading dose of clopidogrel, administered at least 6 hours before PCI,

and/or GP IIb/IIIa antagonists, administered at the time of PCI. (Level of Evidence: C)

6. In patients who have undergone PCI, clopidogrel 75 mg daily should be given for at least 1 month after bare-metal stent implantation (unless the patient is at increased risk for bleeding; then it should be given for a minimum of 2 weeks), 3 months after sirolimus stent implantation, and 6 months after paclitaxel stent implantation, and ideally up to 12 months in patients who are not at high risk of bleeding. (Level of Evidence: B)

Additional guidances incorporating the newer antiplatelet agents have been made available since the release of the original paper. The following are additional clinical guidelines and corresponding links one can go to to learn more details.

- AHA/ASA Guidelines. Guidelines for Prevention of Stroke in Patients with Ischemic Stroke or TIA http://stroke.ahajounrals.org/cgi/content/full/37/2/577
- ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease http://www.americanheart.org/downloadable/heart/1135028673759PAD_Full%20Text.pdf
- AHA/ACC Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease: 2006 Update http://circ.ahajournals.org/cgi/content/full/113/19/2363
- American Diabetes Association Standards of Medical Care in Diabetes http://care.diabetesjournals.org/content/vol29/suppl_1/

III. FDA Approved Indication: The FDA approved indications for the selected antiplatelet agents are shown in Table 1.

Table 1. FDA Approved Indications For Selected Antiplatelet Agents

Agents	Date Approved	FDA Approved Indications	ACS	Post-Stent	Stroke/ TIA	PVD
ASA /extended-release dipyridamole 25 mg/200 mg (Aggrenox®)	11/99	• To reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis			X	
Clopidogrel (Plavix®)	11/97	To reduce the rate of atherothrombotic events as follows: • Recent MI, stroke, or established peripheral arterial disease (approved 11/97) • Acute Coronary Syndrome (unstable angina/non-Q wave MI) including patients who are to be managed medically and those who are to be managed with PCI (with or with/out stent) or CABG. (approved 2/02) • For patients with ST-segment elevation AMI (approved 8/06)	X		X	X
Ticlopidine (Ticlid®)	10/91	• To reduce the risk of thrombotic stroke (fatal or non-fatal) in patients who have experienced stroke precursors or a complete thrombotic stroke • As adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation (approved 3/01)		X	X	

*Information per Package Insert; ASA=aspirin; ACS= acute coronary syndrome; TIA= transient ischemic attack; PVD= peripheral vascular disease; MI=myocardial infarction; PCI=percutaneous coronary intervention.

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-Based Practice Center with input from a statewide committee of experts. Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. For adult patients with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or TIA, or symptomatic peripheral vascular disease do antiplatelets differ in effectiveness?
2. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or TIA, or symptomatic peripheral vascular disease do antiplatelets differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one antiplatelet is more effective or associated with fewer adverse events?

Inclusion Criteria

Adult populations

- Acute coronary syndromes or coronary revascularization via stenting or bypass grafting
- Prior ischemic stroke or TIA
- Symptomatic peripheral vascular disease

Interventions

- Clopidogrel (Plavix®)*
- Ticlopidine (Ticlid®)*
- Extended-Release Dipyridamole and aspirin (Aggrenox®)

* As monotherapy or in combination with aspirin

Outcomes

Studies that measured one or more of the outcomes listed in Table 2 were eligible for the review.

Table 2. Effectiveness outcomes

Populations	Effectiveness outcomes
Acute coronary syndromes or coronary revascularization via stenting or bypass grafting	a. Mortality (all-cause and cardiovascular) b. Cardiovascular events (MI, stroke) c. Invasive vascular procedure failure (including need for additional invasive vascular procedures)

Populations	Effectiveness outcomes
Prior ischemic stroke or TIA	a. Mortality (all-cause and cardiovascular) b. Cardiovascular events (MI, stroke) c. Invasive vascular procedure failure (including need for additional invasive vascular procedures)
Symptomatic peripheral vascular disease	a. Mortality (all-cause and cardiovascular) b. Cardiovascular events (MI, stroke) c. Invasive vascular procedure failure (including need for additional invasive vascular procedures)

Safety outcomes

- Overall adverse effects reported
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events or withdrawals due to specific adverse events (e.g., gastrointestinal, increased bleeding, neutropenia, rash, etc.)

Study designs

- For effectiveness: Head-to-head, controlled clinical trials and systematic reviews
- For safety: in addition to head-to-head, controlled clinical trials, and observational studies including more than 1,000 patients with duration of *at least one year* or that focused on serious and rare adverse events were included in the assessment of adverse events

METHODS

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 (*coronary diseases, coronary procedures, stroke and TIA, peripheral vascular disease*), and included study designs (*randomized controlled trials, systematic reviews*), all limited to human and English language (see Appendix B 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 Pharmaceutcials 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.).

Study Selection

We included English-language reports of randomized controlled trials that evaluated and included the newer antiplatelet agents (extended-release dipyridamole/ASA, clopidogrel, ticlopidine) in patients with ACS, stroke and TIA, and symptomatic PVD, and that reported an included outcome. ST segment elevated MI (STEMI) patients are not covered in this review.

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 ASA therapy. Lastly, trials that specifically utilized Aggrenox® or their components together were included because the components of Aggrenox® are not interchangeable with the individual components of ASA 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 1,000 patients with duration of *at least one 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: study design; setting; population characteristics (including sex, age, ethnicity, diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. We recorded intention-to-treat results if available and if the trial did not report high overall loss to follow-up.

Data were abstracted by one reviewer and checked by a second reviewer. A quantitative analyst abstracted statistical data.

Extraction of Efficacy Data

We abstracted efficacy outcome data from each study. The number of events (for example number of strokes) as well as the number of subjects in each group was collected.

Using this data, we calculated the percent of subjects with each outcome. We also calculated a risk ratio (RR) and 95% confidence interval for each outcome. If the RR was statistically significant (α=0.05), then the number need to treat (NNT) was calculated. To assure that all calculations were performed uniformly across all studies, we calculated all reported statistics (even if the statistics were reported in the publications). Thus, some statistics in this document may vary from those reported in the study publications.

Extraction of Adverse Event Data

Each included study was examined to determine whether it reported data on adverse events. The adverse events were recorded on a spreadsheet that identified each medication group, the description of the adverse event as listed in the original article, and the number of subjects in each group. We then abstracted the number of events or percent of subjects with each adverse event. We assumed that each event represented a unique person.

After abstracting the data, we identified mutually exclusive subgroups of similar events, based on clinical expertise. Our subgroups included: major, minor and non-specified bleeding, thrombocytopenia, leukopenia or neutropenia, other hematological events, liver disorders, other gastrointestinal events, metabolic or endocrine, CNS, rash, cardiovascular or other non-specified vascular events, psychological, musculoskeletal, urological, and other events.

Quality Assessment

The quality of included studies was assessed by evaluating the internal validity (e.g., randomization and allocation concealment; the similarity of compared groups at baseline; specification of eligibility criteria; blinding of assessors, care providers, and patients; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; use of intention-to-treat analysis; post-randomization exclusions) and external validity (e.g., number screened/eligible/enrolled; use of run-in/washout periods or highly selective criteria; use of standard care in control group; source/role of funding; overall relevance).

The trials that had substantial methodological shortcomings in one or more categories were rated poor quality; trials which met all criteria were rated good quality; the remainder were rated fair quality. Because 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 *probably* valid. A "poor quality" trial is not typically valid because the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

The criteria that we used to rate the quality of observational studies of adverse events (See Appendix C) reflect aspects of the study design that are particularly important for assessing adverse event rates. Observational studies were rated as good quality for adverse event assessment if they adequately met six or more of the seven predefined criteria, fair if they met three to five criteria, and poor if they met two or fewer criteria.

Overall quality ratings for the individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Meta-Analysis of Adverse Event Data

In contrast to efficacy, many of the adverse events or side effects of a drug are relatively insensitive to a patient's clinical condition, that is, they are as likely to occur in patients with peripheral vascular disease as they are in patients with prior ischemic stroke or even in patients without the disease in question. For this reason, heterogeneity that precludes statistical pooling of studies regarding efficacy outcomes may not necessarily preclude statistical pooling of adverse event outcomes.

We conducted three sets of analyses. First, we looked at adverse events that occurred in studies comparing an antiplatelet drug to aspirin. We also examined adverse events found in studies with clopidogrel and ticlopidine and studies with clopidogrel plus aspirin and ticlopidine plus aspirin. There were insufficient data to compare any other medications with each other.

For each adverse event subgroup, we reported the number of trials that provided data for any event in the subgroup. If a trial mentioned a particular type of adverse event in the discussion but did not report data on that adverse event, we did not include that trial in that particular event's analysis. In other words, we did not assume zero events occurred unless the trial report specifically stated that zero events were observed. We also reported the total number of individuals in the medication groups who were observed to have experienced the event and the total number of patients in the medication groups in those trials. We then reported the analogous counts for the aspirin group in the relevant trials.

We calculated an odds ratio (OR) for those subgroups that had just one trial. For subgroups of events that had at least two trials, at least one event in the medication group, and at least one event in the aspirin group, we performed a meta-analysis to estimate the pooled odds ratio and its associated 95% confidence interval. Given that many of the events were rare, we used exact conditional inference either to estimate an odds ratio for a single study or to perform the pooling if meta-analysis was warranted, rather than applying the usual asymptotic methods that assume normality. Asymptotic methods require corrections if zero events are observed; generally, half an event is added to all cells in the outcome-by-treatment (two-by-two) table to allow estimation, because these methods are based on assuming continuity. Such corrections can have a major effect on the results when the outcome event is rare. Exact methods do not require such corrections. We conducted the meta-analysis using the statistical software package StatXact.[11]

For the analysis comparing antiplatelet drug to aspirin, any significant pooled odds ratio greater than 1 indicates that the odds of an adverse event associated with the medication are greater than the odds associated with aspirin. For the comparisons between clopidogrel and ticlopidine, an odds ratio greater than 1 implies that the odds of adverse events associated with clopidogrel are greater than those associated with ticlopidine.

RESULTS

Overview

Searches identified 7868 total citations: 641 from the Cochrane Library, 1451 from MEDLINE, and 5759 from EMBASE. Additional review identified 16 citations from reference lists. An additional article was suggested after public review. Four hundred and twenty-seven articles were considered relevant to the topic and screened. Three hundred and fifty-seven

articles were rejected; study design not appropriate (233); no drug reported (68); no drug of interest (19); duplicate data (13); no condition reported (15); duplicate article accidentally ordered (3); no outcome of interest (6).

Sixty-eight articles were included in the drug class review; 36 randomized controlled trials, 7 observational studies; 19 systematic reviews; and 6 studies presenting subgroup results from an included RCT, which are discussed in the text. For Key Question #1 (efficacy), we included 19 randomized controlled trials. For Key Question #2 (safety), we included 35 controlled trials and 6 observational studies. Refer to Figure 1 (Results of Literature Search). Appendix D lists the excluded articles.

The large clinical trials included in this drug review are listed in Table 3.

Table 3. Included Large Clinical Trials

Trial name/ Purpose	Interventions	Description of Patients		Results of Primary Endpoints	
		Study Population	***Follow-up***	***Primary Endpoint***	***Results¶***
Acute Coronary Syndrome (ACS)					
CURE[12] Evaluated the early and long-term efficacy and safety of clopidogrel and aspirin in ACS	C 300 mg x 1 (loading dose) or matching placebo; then C 75 mg + ASA (75-325 mg/d) vs. placebo + ASA (75-325 mg) daily	12,562 ACS patients randomized within 24 hours after onset of symptoms between December 1998 - September 2000 from 482 centers in 28 countries	3-12 months (mean 9 months)	Composite of death from CV causes, nonfatal MI or stroke Composite of those endpoints above plus refractory ischemia	9.3% C vs. 11.4% P RR 0.82, 95% CI 0.73-0.90 p<0.001 16.5%C vs. 18.8% P RR 0.88, 95% CI 0.81-0.95 p<0.001
CHARISMA[13] Evaluated the efficacy and safety of clopidogrel plus aspirin vs. aspirin alone in a broader population of patients with symptomatic or asymptomatic atherothrombosis	C 75 mg per day + low dose ASA (75 mg -162 mg/day) vs. placebo + low-dose aspirin	15,603 patients randomized of which 3,284 (21.0%) had multiple atherothrombotic risk factors; 12,153 (78%) with established CV disease between October 2002 - November 2003 from 768 sites, from 32 countries in 6 continents	18-42 months (median 28 months)	First occurrence of MI, stroke (of any cause), or death from cardiovascular causes (including hemorrhage)	6.8% C vs. 7.3% P RR 0.93, 95% CI 0.83-1.05 p=0.22
Percutaneous Coronary Interventions (PCI)					
CLASSICS[14] Evaluated the safety of ticlopidine compared to clopidogrel (with or without a loading dose) plus ASA in all arms after coronary stenting	T 250 mg twice a day plus ASA 325 mg daily vs. C 75 mg plus ASA 325 mg daily vs. C 300 mg X1 (loading dose) + 325 mg ASA on day 1; then C 75 mg plus ASA 325 mg daily	1020 patients following successful coronary stent procedure between May 1998-November 1998 from 48 centers from 8 European countries	28 days	Major peripheral or bleeding complications, neutropenia, thrombocytopenia, early discontinuation of study drug due to a noncardiac adverse event	9.1% T vs. 6.3% C vs. 2.9% C (loading dose) RR .50, 95% CI .31-.81 p=0.005 in favor of combined clopidogrel groups
PCI-CURE[15] Prospectively designed to test the hypothesis that clopidogrel in addition	After PCI, open-label C or T plus ASA (75-325 mg) x 2-4 weeks then resumed assigned study medication (per CURE trial)	2658 patients undergoing PCI in the CURE trial	30 days with 1 year follow-up	Composite of CV death, MI, or urgent TVR within 30 days of PCI	4.5% C vs. 6.4% P RR 0.70, 95% CI 0.50-0.97 p=0.03

Trial name/ Purpose	Interventions	Description of Patients		Results of Primary Endpoints	
to aspirin before PCI is superior to placebo in preventing major ischemic events afterwards as well as long-term (1 year)	C 75 mg + ASA (75-325 mg/d) vs. placebo + ASA (75-325 mg/d)		(median 8 months)		
CREDO[16] Evaluated the efficacy and safety of long-term clopidogrel therapy with a preprocedural loading dose, both in addition to aspirin prior to elective PCI	C 300 mg X1 (loading dose) or matching placebo + ASA 325 mg 3-24 hours (mean 9.8 hrs) prior to PCI Post-PCI: C 75 mg + ASA 325 mg x 28 days; then C 75 mg daily + ASA (81-325 mg) daily vs. placebo from day 29 through 12 months + ASA (81-325 mg) daily	2116 patients undergoing elective PCI during June 1999 - April 2001 from 99 centers in North America	28 days 1 year	Composite of death, MI, or urgent TVR Composite of death, MI, and stroke	6.8% C (loading dose) vs. 8.3% P RR 0.83 95% CI 0.61-1.11 p=0.23 8.5% C vs. 11.5% P RR 0.73 95% 0.57–0.95 p=0.02
ARMYDA-2[17] Evaluated the efficacy and safety of pretreatment with clopidogrel 600 mg loading dose vs. 300 mg loading dose in improving ischemic complications during coronary intervention	C 600 mg X1 (loading dose) + ASA 100 mg/d vs. C 300 mg x1 (loading dose administered 4-8 hours prior to procedure) + ASA 100 mg/d Post-PCI: C 75 mg daily for up to 1 month (6 months in pts receiving drug-eluting stents and 9 months for ACS) + ASA 100 mg daily	329 pts with stable angina, a positive stress test and an indication for angiography (n=191), or NSTE ACS undergoing angiography (n=64) randomized from March 2004 in 2 centers in Italy	30 days	Composite of death, MI, or TVR up to 30 days after the procedure	4% (high loading dose) vs. 12% (conventional loading dose) RR 0.34, 95% CI 0.13-0.91 p=0.041
Stroke					
ESPS-2[18] Evaluated the efficacy and safety of low dose ASA, extended-release dipyridamole, and the two agents in combination for secondary prevention of ischemic stroke	ASA 25 mg twice a day vs. ERDP 200 mg twice a day vs. ERDP 200 mg /ASA 25 mg twice a day vs. placebo twice a day	6602 patients with prior stroke or TIA within preceding 3 months from 59 clinical centers in 13 European countries between February 1989 - March 1995	2 years	Stroke (fatal and non-fatal) Death Stroke and/or death	12.5% vs.12.8% vs. 9.5% vs.15.2% *RR 0.76, 95% CI 0.63-0.93 *p=0.006 11.0% vs.11.4% vs. 11.2% vs. 12.2% *RR 1.02, 95% CI 0.84-1.23 *p=0.873 20.0% vs. 19.4% vs.17.3% vs. 22.9% *RR 0.87, 95% CI 0.75-1.00 *p=0.048
MATCH[19] Evaluated the hypothesis that clopidogrel in combination with aspirin is superior to clopidogrel alone in high-risk patients with recent TIA or ischemic stroke	C 75 mg plus ASA 75 mg daily vs. C 75 mg plus ASA placebo daily	7599 high-risk patients with a history of a previous ischemic stroke or TIA within 3 months and at least one additional vascular risk factor within the preceding three years and were already receiving clopidogrel 75	18 months	First occurrence of composite ischemic stroke, MI, vascular death or rehospitalization of an acute ischemic event	16% vs. 17% RR 0.94, 95% CI 0.85-1.04 p=0.22

Trial name/ Purpose	Interventions	Description of Patients		Results of Primary Endpoints	
		mg/d. Patients were enrolled between December 2000 - April 2002 from 507 centers (stroke and neurology departments) in 28 countries.			
TASS[20] Evaluated the usefulness of ticlopidine in preventing stroke or death in patients at high risk.	T 250 mg twice a day vs. ASA 650 mg twice a day	3069 patients with recent transient or mild persistent focal cerebral or retinal ischemia during February 1982-May 1986 from 56 centers in North America	2-6 years (Mean 40 months)	Composite of death from all causes or nonfatal stroke	20% vs. 22.7% RR 0.88, 95% CI 0.77-1.01 p=0.048
ESPRIT[21] Evaluated the efficacy and safety of dipyridamole and aspirin with aspirin alone in the secondary prevention of vascular events after cerebral ischemic stroke of presumed arterial origin. The efficacy of "mild anticoagulation" (e.g., target INR 2-3) vs. ASA was also evaluated but not reported in this publication	ERDP/ASA 30-325 mg (mean 75 mg) vs. ASA 30-325 mg (mean 75 mg)	6 months of a TIA (including transient monocular blindness) or minor ischemic stroke or presumed arterial origin between July 1997 - Dec 2005 from 14 countries	3.5 years	Composite of death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complication	12.7% vs. 15.7% RR 0.81, 95% CI 0.67-0.97 p=0.024
Predefined Group of Vascular Conditions Including Peripheral Vascular Disease					
CAPRIE[22] Evaluated the efficacy and safety of clopidogrel compared to aspirin in reducing the risk of ischemic stroke, MI or vascular death in subgroups of patients with atherosclerotic vascular disease	C 75 mg + ASA placebo vs. ASA 325 mg + C placebo daily	19,185 patients comprised of subgroups with a recent ischemic stroke, recent MI, or symptomatic peripheral arterial disease between March, 1992-February 1996 from 384 centers from 16 countries	1-3 years (Mean 1.91 years)	Composite of first occurrence of ischemic stroke, MI or vascular death	5.32% C vs. 5.83% A RR 0.91,95% CI 0.3-16.5 p=0.043

ASA = aspirin; ERDP = extended-release dipyridamole; C = clopidogrel; T = ticlopidine; P= placebo; TVR = total vessel revascularization; CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; RR = relative risk; PCI = percutaneous coronary intervention; NS = not significant; *All RR and p values based on ERDP/ASA vs. ASA. ¶Statistics were performed by RAND and may differ slightly than what is reported in study publication.

Key Question 1. Effectiveness

For adult patients with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or TIA, or symptomatic peripheral vascular disease, do antiplatelets differ in effectiveness?

Key Question 1a. Outcomes: Acute Coronary Syndrome

In patients with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, what is the comparative efficacy of the newer antiplatelet agents in mortality (all-cause and cardiovascular), cardiovascular events (MI, stroke), invasive vascular procedure failure (including need for additional invasive vascular procedures)?

Overall summary of evidence for comparative effectiveness and safety outcomes of the newer antiplatelet agents in patients with acute coronary syndrome (ACS)

The largest body of evidence exists for clopidogrel in patients with ACS. No patient data exist for the efficacy and safety with ticlopidine and ERDP/ASA in the setting of ACS.

Efficacy Trials: (ACS)

- **Head-to-head trials**: No trials of the newer antiplatelet agents in ACS were identified.

- **Active-controlled trials:** Two good-quality, multicenter randomized controlled trials (RCTs); CURE[12] and CHARISMA[13] were evaluated.

The CURE[12] trial compared the efficacy and safety of clopidogrel and aspirin in 12,562 patients hospitalized within 24 hours of the onset of chest pain with diagnosis of ACS. Initial inclusion criteria allowed for patients > 60 years of age who had a history of coronary artery disease but no acute ECG changes. After the first 3000 patients were enrolled, only patients with myocardial necrosis or ECG 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.[23] Patients enrolled in the CURE[12] trial were from centers that tended to favor a conservative approach to the treatment of ACS, so the usage rates of other modalities, such as angiography, PCI, and GP IIb/IIIa agents, were typically lower than the rates at many U.S. centers. Nevertheless[24], clopidogrel plus aspirin reduced the rates of the combined endpoint of death from CV causes, nonfatal MI, or stroke more than aspirin alone (9.3% vs. 11.4%; p<0.001) for an absolute benefit of 2.1%. That benefit was associated with a higher risk of bleeding. This study reported a ~45% and a ~20% temporary and permanent discontinuation rate of the study medications, respectively. The most common reason for temporarily discontinuing the study medication was the need for revascularization or another surgical procedure.

Clopidogrel plus ASA was beneficial in patients with acute coronary syndrome without ST segment elevation in reducing the rates of death from CV causes, nonfatal MI or stroke compared to placebo plus ASA. This benefit of clopidogrel was observed within 24 hours after randomization in the first primary outcome and was statistically significant for the secondary primary endpoints.

Primary Outcomes: clopidogrel + ASA vs. placebo + ASA

- Composite endpoint death from CV causes, nonfatal MI, or stroke, or: 9.3% vs. 11.4%; RR 0.82, 95% CI 0.73-0.90; p<0.001

- Composite endpoint of death from CV causes, nonfatal MI, stroke, or refractory ischemia: 16.5% vs. 18.8%, RR 0.88, 95% CI 0.81-0.95; p<0.001

Significantly fewer patients in the clopidogrel group compared to the placebo group had severe ischemia or recurrent angina. Radiologic evidence of heart failure was found in fewer patients in the clopidogrel group compared to the placebo group. Slightly fewer patients in the clopidogrel group underwent coronary revascularization during the study, but the difference was due entirely by the rate of revascularization during the initial period of hospitalization.

Secondary Outcomes: clopidogrel + ASA vs. placebo + ASA

- Severe ischemia: 2.8% vs. 3.8%; RR 0.74, 95% CI 0.61-0.90; p=0.003
- Heart failure: 3.7% vs. 4.4%; RR 0.82, 95% CI 0.69-0.98; p=0.026
- Need for revascularization: 20.8% vs. 22.7%; RR 0.92, 95% CI 0.86-0.98; p=0.03
- Recurrent angina: 20.9% vs. 22.9%; RR 0.91, 95% CI 0.85-9.98; p=0.01

The CHARISMA[13] trial demonstrated no significant benefit with clopidogrel plus aspirin as compared with placebo plus aspirin in reducing the incidence of the primary endpoint of MI, stroke, or death from cardiovascular causes in patients with stable cardiovascular disease or multiple cardiovascular risk factors. In the CHARISMA[13] trial, the subgroup that appeared to benefit from the therapy were the "symptomatic" group or the patients with established vascular diseases (e.g., myocardial infarction or transient ischemic attack/ischemic stroke within past 5 years or those with a history of multivessel coronary disease and/or multivessel revascularizations or those with symptomatic peripheral arterial disease and an ABI of ≤ 0.85). The subgroup (asymptomatic group) having multiple risk factors and/or distant vascular events that did not meet the inclusion criteria for established vascular diseases appeared to have potentially worse outcomes. As with all subgroup analyses, these findings should be interpreted cautiously.

Primary Outcome: clopidogrel + ASA vs. placebo + ASA

- First occurrence of myocardial infarction, stroke (of any cause), or death from cardiovascular causes (including hemorrhage): 6.8% vs. 7.3%; RR 0.93, 95% CI 0.83-1.05); p=0.22

There was a moderate, benefit in reducing the secondary composite endpoint with clopidogrel plus ASA compared to placebo and ASA.

Secondary Outcome: clopidogrel + ASA vs. placebo + ASA

- First occurrence of myocardial infarction, stroke, death from CV causes, or hospitalization for unstable angina, transient ischemic attack, or a revascularization procedure: 16.7% vs. 17.9%; RR 0.93, 95% CI 0.87-0.995; p=0.049

- **Meta-analyses**

Two meta-analyses[25,26] were included that evaluated the reduction of clopidogrel and ticlopidine in patients at high risk of vascular disease. Both meta-analyses reported that clopidogrel and ticlopidine were associated with a modest, yet statistically significant, reduction

in the odds of serious vascular events (stroke, myocardial infarction or vascular death) compared to aspirin (12.0% vs. 13%; OR 0.91, 95% CI 0.84-0.98; p=0.01) in patients at high risk for serious vascular events. This reduction means that 11 serious vascular events are avoided per 1000 patients following ~ 2 years of therapy when treated with a thienopyridine (clopidogrel or ticlopidine) rather than aspirin.

No comparative conclusion between the newer antiplatelet agents is available in the setting of ACS. The overall rating of clopidogrel is good in this population.

Safety/Adverse Events:

- **Active -controlled trials**:

In the CURE[12] trial, adding clopidogrel to aspirin provided benefit regardless of the aspirin dose but with a higher incidence of bleeding. For patients with ACS, a statistically significant higher incidence of major bleeding occurred in the clopidogrel and aspirin group compared to the placebo plus aspirin group, yielding a 38% increase in major bleeding complications (p=0.001). A nonsignificant higher incidence of life-threatening bleeding occurred in the clopidogrel group. Minor bleeding episodes were twice as common with clopidogrel than with placebo. A post-hoc analysis[23] from the CURE trial suggests that lower aspirin doses (75-100 mg) with clopidogrel have a more favorable safety profiles in terms of bleeding rates compared to when clopidogrel was combined with higher doses of aspirin.

Clopidogrel + ASA vs. placebo + ASA
- Major bleeding: 3.7% vs. 2.7%; RR 1.38, 95% CI 1.13-1.67; p=0.001
- Life- threatening bleeding: 2.2% vs. 1.8%; RR 1.21, 95% CI 0.95-1.56; p=0.125
- Non-life-threatening bleeding: 1.5% vs. 0,9%; RR 1.70, 95% CI 1.22-2.35; p=0.002
- Minor bleeding: 5.1% vs. 2.4%; RR 2.12, 95% CI 1.75-2.56; p<0.001

The CHARISMA[13] trial resulted in an increased trend of severe bleeding associated with dual antiplatelet therapy (clopidogrel + ASA) compared to placebo, at 1.7% vs. 1.3% respectively; p=0.09. Among the subgroup of asymptomatic patients, severe bleeding was 2.0% with clopidogrel and 1.2% with placebo (p=0.07); while the corresponding rate among the symptomatic patients (established cardiovascular disease) was 1.6% and 1.4% respectively; p=0.39. The rate of moderate bleeding in the asymptomatic group was increased but not statistically significant; p=0.08. The rate for moderate bleeding in the symptomatic group was significant and reported as 2.1% with clopidogrel compared to 1.3% in the placebo group; p<0.001. No significant increases in intracranial or fatal bleeding were observed.

Clopidogrel + ASA vs. placebo + ASA
- Severe bleeding: 1.7% vs. 1.3%; RR 1.25, 95% CI 0.97-1.61; p=0.087
- Moderate bleeding: 2.1% vs. 1.3%; RR 1.62, 95% CI 1.27-2.08; p<0.001

If aspirin is chosen as the principal antiplatelet agent and upper GI bleeding occurs, a recent randomized controlled study[27] found that for patients in this situation, low-dose aspirin

plus a proton pump inhibitor led to fewer subsequent GI bleeding episodes than clopidogrel alone (8.6% vs. 0.7%; p = 0.001).

Subgroups:

No conclusion about the comparative effectiveness or safety of the newer antiplatelet agents based on age, gender, race, comorbidities or other medications can be made from this body of evidence in patients with ACS.

Overall summary of evidence for comparative effectiveness and safety of the newer antiplatelet agents in patients with PCI

Efficacy Trials: (PCI)

The largest body of evidence exists for clopidogrel in patients undergoing PCI. No data exists for extended-release dipyridamole/aspirin (ERDP/ASA) in patients undergoing PCI.

- **Head-to-head**: Eight trials were identified, only one[14] of which was judged to be of good quality.

The 28 day CLASSICS[14] trial was primarily a safety study evaluating ticlopidine in combination with aspirin vs. clopidogrel 75mg (without loading dose) vs. clopidogrel 75mg (with 300 mg loading dose) in combination with aspirin. 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. The risk of an event in the clopidogrel loading-dose group was about a third of that compared to the ticlopidine patients.

Primary Outcomes: ticlopidine 250mg twice a day vs. clopidogrel 75 mg (no loading dose) vs. clopidogrel 75 mg (with 300mg loading dose)

- Composite of any of the below endpoints: 9.1% vs. 6.3% vs. 2.9% (4.6% for both clopidogrel groups compared to ticlopidine, RR .50, 95% CI .31-.81; p=0.005)
- Major peripheral or bleeding complications: 1.2% vs. 1.2% vs. 1.5%
- Neutropenia: 0.3% reported with ticlopidine. None reported in the clopidogrel groups.
- Thrombocytopenia: None reported with ticlopidine. 0.6% reported in both clopidogrel groups.
- Early discontinuation of study drug because of a noncardiac adverse event (including death of noncardiac origin): 8.2% vs. 5.1% vs. 2%

Numerous secondary outcomes were evaluated in the CLASSICS[14] trial including major adverse clinical events (MACE) defined as MI (fatal and non-fatal), target lesion revascularization (TLR), and sudden death. The 30-day rate for MACE was similar between ticlopidine and to the combined clopidogrel groups ($p \geq 0.538$).

Secondary Outcome: ticlopidine 250mg twice a day vs. clopidogrel 75 mg (no loading dose) vs. clopidogrel 75 mg (with 300mg loading dose)

- MACE: 0.9% vs. 1.5% vs. 1.2% (p=NS for all comparisons)

- **Active-controlled trials**: Three good-quality, multicenter randomized controlled trials[15-17] in patients with PCI were evaluated.

The PCI-CURE[15] trial was a predefined substudy of the CURE population that evaluated the outcomes of patients undergoing PCI. This study examined the role of clopidogrel prior to (mean of 6 days before intervention) and after PCI. PCI-CURE[15] trial found that with long-term (8 months on average) administration of clopidogrel and aspirin after PCI, the rates of CV death, MI, or any revascularization were lower.

Primary Outcome: clopidogrel vs. placebo

- Composite of CV death, MI, or urgent target-vessel revascularization within 30 days of PCI: 4.5% vs. 6.4%; RR 0.70, 95% CI 0.50-0.97; p=0.03

Secondary Outcome: clopidogrel vs. placebo

- CV death or MI from PCI to end of trial: 6.0% vs. 8.0%; RR 0.75, 95% CI 0.56-1.00; p=0.047

The CREDO[16] trial demonstrated a long-term (1-year) reduction in CV events in patients undergoing PCI with clopidogrel and aspirin. Pretreatment loading dose of clopidogrel 300mg ≥ 6 hours prior to PCI 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 benefit of early pretreatment and the lack of benefit when pretreatment clopidogrel was administered less than 6 hours before treatment occurred in all subgroups. This study was limited by ~40% of the patients not completing the study drug treatment for one year with either the active medication or placebo.

Primary Outcomes: clopidogrel vs. placebo

1-year outcome

- Composite of death, MI, or stroke: 8.5% vs. 11.5%; RR 0.73, 95% CI 0.57-0.95; p=0.021

28-day outcome

- Composite of death, MI, or urgent TVR: 4.5% vs. 6.4%; RR 0.70, 95% CI 0.50-0.97; p=0.03

Secondary Outcomes: clopidogrel vs. placebo

- Any major bleeding events at 1 year (intent-to-treat population): 8.8% vs. 6.7%; p =0.07
- Any major bleeding events at 28 days (intent-to-treat population): 4.7% vs. 3.6%; p=0.19
- Early discontinuation of study drugs at 1 year (intent-to-treat population): 37% vs. 39%; p=0.821
- Early discontinuation of study drugs at 28 days: 5.5% vs. 4.8%; p=0.473

The ARMYDA-2[17] study demonstrated that pretreatment with a 600 mg clopidogrel loading dose reduces periprocedural MI in relatively low-risk patients with stable angina or experiencing a NSTE ACS undergoing a coronary angiography. In a multivariable analysis, pretreatment with the 600 mg loading dose of clopidogrel was an independent predictor of decreased risk of periprocedural myocardial infarction (OR 0.48, 95% CI 0.15-0.97l; p=0.044).

The study supports that the administration of clopidogrel 600 mg loading dose at least 4 to 8 hours before intervention is acceptable and can be considered when an optimal pre-procedural timing for clopidogrel 300 mg loading dose prior to PCI is not feasible. The bleeding risk associated with emergency CABG with a higher loading dose requires further evaluation.

Primary Outcome: clopidogrel 600 mg (loading dose) vs. clopidogrel 300 mg (loading dose)

- Occurrence of death, myocardial infarction, or total vessel revascularization up to 30 days after procedure: 4% vs. 12%; p=0.041

Numerous secondary outcomes were evaluated in the ARMAYDA-2[17] study including postprocedural increase of markers of myocardial injury above upper normal limits. Although, myocardial injury markers are not of interest to this review, the results are reported below for completeness. No patients in either group experienced postprocedural major bleeding or required transfusions. Minor bleeding was observed in one patient in each clopidogrel group.

Secondary Outcomes: clopidogrel 600 mg (loading dose) vs. clopidogrel 300 mg (loading dose)

- Postprocedural increase of CK-MB: 14% vs. 26%; p=0.036
- Postprocedural increase of troponin I: 26% vs. 44%; p=0.004
- Postprocedural increase of myoglobin: 30% vs. 46%; p=0.015
- Major bleeding: Not observed in either groups
- Minor bleeding: 1 pt in each clopidogrel group (total of 2 patients)
- Entry-site complications: 9 patients vs. 6 patients, p=0.56
- Thrombocytopenia: Not observed in either groups

- **Meta-analyses**

Two meta-analyses[28 29] which compared clopidogrel and ticlopidine following stent placement procedure were included. The meta-analysis performed by Casella et al.[28] found that clopidogrel was superior to ticlopidine in reducing the 30-day combined endpoint of death and non-fatal MI. The second meta-analysis conducted by Bhatt et al.[29] found that clopidogrel was at least as efficacious as ticlopidine in reducing major adverse cardiac events. However, both meta-analyses included observational (registry) data in their pooled analyses. When the pooled analyses were restricted to data from randomized trials, the difference between ticlopidine and clopidogrel was no longer statistically significant.

The overall rating of clopidogrel is good in this population.

Safety/Adverse Events:

Based on adverse event profiles, clopidogrel alone is safer than ticlopidine. In a pooled analysis, clopidogrel with ASA was associated with a higher incidence of bleeding than aspirin (see Table 22). There is insufficient data available to determine if the bleeding incidence with ticlopidine in combination with ASA is higher compared to aspirin alone. Thienopyridines were associated with diarrhea and rash more often than was aspirin (see Table 22). Clopidogrel had fewer serious hematological adverse effects than ticlopidine, particularly in regard to neutropenia

and thrombotic thrombocytopenic purpura (TTP). Ticlopidine had significantly more other GI and rash events compared to clopidogrel (see Table 23).

- **Head-to-Head Trial**:

In the CLASSICS trial[14] 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% ticlopidine group and 0.7% in 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; three of them had received heparin concomitantly. Ticlopidine and clopidogrel had relatively similar adverse effects profile but there were notable differences. Rash and diarrhea were the most common reasons to stop ticlopidine, more so than with clopidogrel in the PCI trials. The incidence of neutropenia associated with ticlopidine has not been noted to the same degree with clopidogrel.

ticlopidine vs. clopidogrel 75 mg vs. clopidogrel 300 mg/75 mg

- Major peripheral or bleeding complication: 1.2% vs. 1.2% vs. 1.5%
- Skin disorder: 2.6% vs. 0.9% vs. 0.6%
- Neutropenia: 0.3% vs. 0 vs. 0
- Thrombocytopenia: 0 vs. 0.6% vs. 0.6%
- Gastrointestinal disorder: 2.6% vs. 2.4% vs. 0.3%
- Allergy: 1.2% vs. 0 vs. 0

- **Active-Controlled Trials:**

In the PCI-CURE[15] trial, no significant difference in major, minor or life-threatening bleeding was seen between clopidogrel and aspirin at 30 days. At end of follow-up, (average, 8 months) the only statistical significant difference in bleeding for clopidogrel compared to aspirin was minor bleeding episodes.

PCI to 30 days: clopidogrel vs. placebo

- Major bleeding: 1.6% vs. 1.4%; RR 1.13, 95% CI 0.61-2.10; p=0.69
- Life-threatening bleeding: 0.7% vs. 0.7%; RR 0.92, 95% CI 0.38-2.26; p=0.86
- Non-life threatening bleeding: 0.9% vs. 0.7%; RR 1.37, 95% CI 0.58-3.23; p=0.48
- Minor bleeding: 1.0% vs. 0.7%; RR 1.33. 95% CI 0.59-3.03; p=0.49

PCI to follow-up: clopidogrel vs. placebo

- Major bleeding: 2.7% vs. 2.5%; RR 1.12, 95% CI 0.70-1.78; p=0.64
- Life-threatening bleeding: 1.2% vs. 1.3; RR 0.91, 95% CI 0.47-1.78); p=0.78
- Non-life threatening bleeding: 1.5% vs. 1.1%; RR 1.37, 95% CI 0.70-2.66; p=0.36
- Minor bleeding: 3.5% vs. 2.1%; RR 1.68, 95% CI 1.06-2.68; p=0.03

In the CREDO[16] study, reasons why patients (n=94) discontinued study medications prior to PCI were not provided. Following the PCI 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). A nonsignificant increase in the risk of major bleeding at 1 year occurred.

1-year Intent-to-Treat Population: clopidogrel vs. placebo
- Major bleeding (any): 8.8% vs. 6.7%; p=0.07
- Minor bleeding (any): 5.3% vs. 5.6%; p=0.84

28 day Intent-to-Treat Population: clopidogrel vs. placebo
- Major bleeding (any):4.7% vs. 3.6%; p=0.19
- Minor bleeding (any): 3.1% vs. 2.3%; p=0.23

Subgroups:

No conclusion about the comparative effectiveness or safety of the newer antiplatelet agents based on age, gender, race, comorbidities or other medications can be made from this body of evidence in patients undergoing PCI.

Acute Coronary Syndrome (ACS)

- **Head-to-Head Trials:** Relevant head-to-head trials were not identified.

- **Active-controlled Trials**: (good quality)

One active-controlled trial of good quality, Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events Trial (CURE),[12 30] evaluated the early and long-term efficacy and safety of clopidogrel and aspirin in 12,562 patients. Patients were randomized within 24 hours of hospitalization to clopidogrel 300 mg loading dose, 75 mg daily thereafter, with ASA (n=6259); or placebo with ASA (n=6303) for 3–12 months (mean, 9 months). The aspirin dose ranged from 75 to 325 mg daily in both groups (median dose, 150 mg).[23]

Another active-controlled trial of good quality, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA)[13] trial evaluated the efficacy and safety of clopidogrel plus low dose aspirin (75 mg-162 mg/day) compared with low-dose aspirin in patients at high risk for a cardiovascular event. The CHARISMA trial was a randomized, double-blind, placebo-controlled trial. Patients enrolled in the established cardiovascular group had either documented coronary disease (e.g., angina with documented multivessel coronary disease, history of multivessel PCI, history of multivessel CABG, MI during previous 5 years), documented cerebrovascular disease, (e.g., TIA or ischemic stroke during previous 5 years) or documented symptomatic peripheral arterial disease (e.g., current intermittent claudication and akle-brachial index ≤ 0.85, history of intermittent claudication and previous intervention including amputation, peripheral bypass, or angioplasty) and were designated "symptomatic." Those patients who were enrolled because of multiple atherothrombotic risk factors without documented cardiovascular disease were designated "asymptomatic." (See Table 4). A small number of participants categorized as "asymptomatic" had events and/or interventions although they did not meet the inclusion criteria for established cardiovascular disease (see footnote below Table 4 for further details). The time duration

following the qualifying ischemic event to randomization in the symptomatic patients was a median of 23.3, 3.5, 2.7, 23.3 months for myocardial infarction; stroke; TIA; and PAD, respectively.[31]

Table 4. CHARISMA Trial[13] Primary Inclusion Criteria

[31]*Primary Inclusion Criteria*	n=15603, n (%)
Patients with Multiple Atherothrombotic Risk Factors (Asymptomatic)¶	3284 (21.0)
Major Risk Factors	3025 (19.4)
Type 1 or 2 diabetes (with drug therapy)	2655 (17.0)
Diabetic nephropathy	1403 (9.0)
Ankle-brachial index <0.9	186 (1.2)
Asymptomatic carotid stenosis ≥ 70% of luminal diameter	255 (1.6)
≥1 Carotid plaque, as evidenced by intima-media thickness	411 (2.6)
Minor Risk Factors	2928 (18.8)
Systolic blood pressure ≥150 mm Hg, despite therapy for at least 3 mo	1553 (10.0)
Primary hypercholesterolemia	2023 (13.0)
Current smoking >15 cigarettes/day	555 (3.6)
Male sex and age ≥65 yr or female sex and age ≥70 yr	1694 (10.9)
Patients with established Cardiovascular Disease (Symptomatic)	12153 (77.9)
Documented Coronary Disease	5835 (37.4)
Angina with documented multivessel coronary disease	1773 (11.4)
History of multivessel PCI	832 (5.3)
History of multivessel CABG	1469 (9.4)
Myocardial Infarction	3846 (24.6)
Documented Cerebrovascular Disease	4320 (27.7)
Transient ischemic attack during previous 5 year	1233 (7.9)
Ischemic stroke during previous 5 yr	3245 (20.8)
Documented Symptomatic Peripheral Arterial Disease	2838 (18.2)
Current intermittent claudication and ankle-brachial index ≤0.85	1777 (11.4)
History of intermittent claudication and previous intervention (e.g., amputation, peripheral bypass, or angioplasty)	1636 (10.5)

* patients were required to have 2 major or 3 minor or 1 major and 2 minor atherothrombotic risk factors; **patients were required to have one of the listed conditions; ¶ 10.4% had a prior MI, 5.8% with a prior stroke, 5.2% with prior TIA, 7.7% had undergone a PCI, and 9.8% had a previous CABG. Data on 166 enrolled were not adequately differentiated per medical records.

Mortality (all-cause and cardiovascular)

There were fewer deaths from cardiovascular causes, a secondary endpoint in CURE,[12] with clopidogrel than with placebo, but this was not statistically significant (5.1% versus 5.5%; RR 0.93, 95% CI 0.80-1.10; p=0.325). (See Table 6)

In CHARISMA,[13] while total mortality and cardiovascular mortality did not differ significantly among the two groups overall, the rates of the individual component of death from any cause were higher with clopidogrel 5.4% vs. 3.8% in the placebo group for the asymptomatic group; p=0.04. Likewise, death from CV causes was higher with clopidogrel compared to placebo (3.9% vs. 2.2%) in the asymptomatic group; p=0.01.(See Table 5) These subgroup analyses should be viewed cautiously, however.

Combined Outcomes (fatal and non-fatal)

Two primary endpoints in CURE[12] were available: (1) the composite of death from cardiovascular causes, nonfatal myocardial infarction or stroke; and (2) the composite of those endpoints plus refractory ischemia. The first primary endpoint occurred in 9.3% of clopidogrel patients compared to 11.4% of placebo patients (RR 0.82, 95% CI 0.73-0.90; p<0.001). The relative risk (RR) was statistically significant for clopidogrel plus aspirin over placebo plus aspirin for the second primary endpoint (16.5% vs. 18.8%; RR 0.88, 95% CI 0.81-0.95; p<0.001). The benefit of clopidogrel was observed within 24 hours after randomization in the first primary outcome and was statistically significant for the second primary endpoint (1.4% for clopidogrel vs. 2.1% for placebo (RR 0.66, 95% CI 0.51-0.86; p<0.003). By 30 days, the RR for the first primary endpoint was significant for clopidogrel compared to placebo (4.3% vs. 5.4%; RR 0.79, 95% CI 0.67-0.92; p=0.003) and remained significant for the second primary outcome. A relative reduction of 19% for the first primary outcome favoring clopidogrel plus aspirin over placebo and aspirin was observed (95% CI 0.73-0.90; p<0.001). A significant RRR (18%) remained for the primary outcome (death from CV causes, nonfatal MI or stroke) from day 31 through 12 months (p= 0.009). During any periods of the study, the number of major vascular events prevented was greater than the risk of bleeding requiring intervention for clopidogrel in ACS compared to placebo. However, the significant differences in favor of clopidogrel were observed early on during 0 to 1 and 1 to 3 months compared to the other treatment periods 3 to 6, 6 to 9, and 9 to 12 months.[32]

A post hoc observational analysis[23] of CURE showed favorable results when clopidogrel was added in the subset of patients taking different doses of ASA: low dose ≤ 100 mg (n=5320), medium dose 101 to 199 mg (n=3109), and high dose ≥ 200 mg (n=4110). The combined incidence of from CV causes, nonfatal MI, or stroke (first primary outcome) was reduced from 13.6% to 9.8% (RR 0.71, 95% CI 0.59-0.85), with clopidogrel plus high-dose aspirin compared to high-dose aspirin alone. The incidence of the first primary endpoint continued to decrease for clopidogrel with each subsequent lowering of the ASA dose, 9.8% to 9.5% (RR 0.97, 95% CI 0.77-1.22) compared to medium-dose ASA and 10.5% vs. 8.6% (RR 0.81, 95% CI 0.68-0.97) compared to low-dose ASA alone. Similar results were observed with the second primary endpoint.

During the median of 28 months, the rate of the primary efficacy endpoint (first occurrence of MI, stroke, or death from CV) in the CHARISMA[13] trial was 6.8% in the clopidogrel group and 7.3% in the placebo group (RR 0.93, 95% CI 0.83–1.05; p=0.22). The rate of the principal secondary efficacy endpoint (first occurrence of MI, stroke, death from CV, or hospitalization for unstable angina, TIA, or a revascularization procedure) was 16.7% in the clopidogrel group compared with 17.9% in the placebo group (RR 0.92, 95% CI 0.86-0.995; p=0.04). In a subgroup analyses, which should be interpreted cautiously, demonstrated that the rate of the primary endpoint among the asymptomatic patients was 6.6% with clopidogrel and 5.5% with placebo (RR 1.2, 95% CI 0.91 – 1.59; p=0.20). In the subgroup with clinically evident atherothrombosis, the rate of the primary endpoint was 6.9% with clopidogrel and 7.9% with placebo (RR 0.88, 95% CI 0.77-0.998; p = 0.046). (See Table 5).

Table 5. CHARISMA[13] Trial: Composite and Individual Endpoints

Endpoint	C+ ASA (n=7802) no. (%)	P + ASA (n=7801) no. (%)	RR (95% CI)	P value	NNT
Primary: First occurrence of myocardial infarction, stroke, or death from cardiovascular causes	534 (6.8)	573 (7.3)	0.93 (0.83-1.04)	0.22	NS
Symptomatic Group* (n=12,153)	6.9	7.9	0.88 (0.77-0.998)	0.046	100
Asymptomatic Group* (n=3284)	6.6	5.5	1.20 (NR)	0.20	NS
Death from any cause	371 (4.8)	374 (4.8)	0.99 (0.86-1.14)	0.90	NS
Symptomatic Group* (n=12,153)	NR	NR	NR	NR	NS
Asymptomatic Group* (n=3284)	5.4	3.8	NR	0.04	63
Death from cardiovascular causes	238 (3.1)	229 (2.9)	1.04 (0.87-1.24)	0.68	NS
Symptomatic Group* (n=12,153)	NR	NR	NR	NR	NR
Asymptomatic Group* (n=3284)	3.9	2.2	NR	0.01	59
Myocardial infarction (nonfatal)	146 (1.9)	155 (2.0)	0.94 (0.75-1.18)	0.59	NS
Ischemic stroke (nonfatal)	132 (1.7)	163 (2.1)	0.81 (0.65-1.02)	0.07	NS
Stroke (nonfatal)	150 (1.9)	189 (2.4)	0.79 (0.64-0.98)	0.03	200
Secondary: first occurrence of myocardial infarction, stroke, death from cardiovascular causes, hospitalization for unstable angina, TIA, or a revascularization procedure (coronary, cerebral, or peripheral)	1301 (16.7)	1395 (17.9)	0.92 (0.86-0.995)	0.04	83
Hospitalization for unstable angina, transient ischemic attack, or revascularization	866 (11.1)	957 (12.3)	0.90 (0.83-0.99)	0.02	86

ASA=aspirin; C= clopidogrel; P=placebo; RR=Relative Risk; CI=confidence interval; TIA=transient ischemic attack; NR=Not reported; NS=Not Significant. * Prespecified sub group analyses

Cardiovascular events (MI, stroke)

In CURE,[12] rates of the individual components of the composite endpoint were lower in the clopidogrel group. Significant differences in the RR were observed for two individual endpoints: MI (specifically Q-wave MI), and refractory ischemia during hospitalization. The incidence of MI for clopidogrel compared to placebo at 12 months was 5.2% and 6.7%, respectively (RR 0.78, 95% CI 0.68-0.90; p <0.001), which corresponds to a NNT of 68. (See Table 6 for the incidence of Q-wave MI.) The component refractory ischemia event (first ischemic event during initial hospitalization) occurred in 85 patients with clopidogrel compared to 126 patients in the placebo group (RR 0.68, 95% CI 0.52-0.89; p=0.007).

In CURE[12], a 14% risk reduction (NS) was seen in the incidence of stroke with clopidogrel and ASA compared to placebo and ASA (1.2% vs. 1.4%) (RR 0.87, 95% CI 0.64-1.18). (Details of the CURE[12] trial are included in Evidence Table A1 and Quality Table A2). Additional outcomes from the CURE[12] trial are presented in Table 6.

Table 6. Outcomes from CURE[12] trial

Outcomes at 12 months	Clopidogrel + ASA (n=6259) no. (%)	Placebo + ASA (n=6303) no. (%)	Relative Risk (95% CI)
First primary outcome: Nonfatal MI, stroke or cardiovascular death	582 (9.3)	719 (11.4)	0.82 (0.73-0.90)
Second primary outcome: First primary outcome or refractory ischemia¶	1035 (16.5)	1187 (18.8)	0.88 (0.81-0.95)
Cardiovascular mortality	318 (5.1)	345 (5.5)	0.93 (0.80-1.10)
Myocardial Infarction† Q-wave Non-Q wave	324(5.2) 116 (1.9) 216 (3.5)	419 (6.7) 193 (3.1) 242 (3.8)	0.78 (0.68-0.90) 0.61 (0.48-0.76) 0.90 (0.75-1.08)
Stroke	75 (1.2)	87 (1.4)	0.87 (0.64-1.18)
Refractory ischemia* During initial hospitalization§∞ After discharge¶	544 (8.7) 85 (1.4) 459 (7.6)	587 (9.3) 126 (2.0) 461 (7.6)	0.93 (0.83-1.04) 0.68 (0.52-0.90) 0.99 (0.87-1.13)
Other severe ischemia∞	176 (2.8)	237 (3.8)	0.74 (0.61-0.90)
Other recurrent angina∞	1307 (20.9)	1442 (22.9)	0.91 (0.85-0.98)
Revascularization procedure∞	1302 (20.8)	1431 (22.7)	0.92 (0.86-0.98)
Radiologic evidence of heart failure∞	229 (3.7)	280 (4.4)	0.82 (0.69-0.98)

CI denotes confidence interval.¶ Refractory ischemia after hospital discharge = rehospitalization for unstable angina with ECG changes; † Some patients had both Q-wave and non-Q wave MI; *Only the first ischemic event was counted for each patient; §Refractory ischemia during hospitalization = recurrence of angina with new ECG changes despite optimal antianginal and antithrombotic therapy that required an emergent intervention or transfer for an intervention within 24 hours; ∞ proportions of patients who had events other than those included in the first primary outcome while they were in the hospital.

In the CHARISMA[13] trial, the rate of the individual component nonfatal myocardial infarction did not reach statistical significance between clopidogrel plus ASA vs. placebo plus ASA, 1.9% vs. 2.0%; RR 0.94, 95% CI 0.75-1.18; p=0.59, respectively. (Refer to Table 5.) In addition, the rate of the individual component nonfatal ischemic stroke did not reach statistical significant between clopidogrel plus ASA vs. placebo plus ASA, 1.7% vs. 2.1%; RR 0.81 (0.65-1.02. The incidence of nonfatal stroke in the same study was 1.9% in the clopidogrel plus ASA vs. 2.4% in the placebo plus ASA, RR 0.79 (0.64-0.98).

Invasive vascular procedure failure (including need for additional invasive vascular procedures)

In CURE,[12] angiography and any corresponding interventions were based on the discretion of the treating physician and not in a randomized controlled fashion. Coronary artery bypass graft overall was performed in 16.5% of patients at a median time of >3 months after

randomization.[33] Fewer patients on clopidogrel compared to placebo had coronary revascularization procedures during the study (36% vs. 36.9%), but that did not reach statistical significance. The difference in the incidence was attributable to revascularization procedures during the initial period of hospitalization (clopidogrel group 20.8%, placebo group 22.7%, p=0.03).

A post-hoc observational study[23] from the CURE trial evaluated various aspirin regimens with clopidogrel. The overall incidence of percutaneous coronary intervention (PCI) procedures was 19.9%, 17.3%, and 25.9% (p<0.0001) with low-, medium-, and high-dose aspirin, respectively. A subgroup analysis[15 34] from the PCI-CURE trial reported that the need for a second revascularization was lower in the clopidogrel group than the placebo group, 17.4% vs. 14.2%; (RR 0.82, 95% CI 0.68-1.00; p=0.049). This benefit was mainly due to the reduced need for a repeat PCI in the clopidogrel group compared to the placebo group, 10.7% vs. 12.9%; (RR 0.83, 95% CI 0.66-1.03).

Systematic Review:

Tran et al.[35] evaluated the antiplatelet treatment for ACS (n=59,821), as well as for CVA (n=30619) and PAD (n=9214), in a systematic review that included 111 trials. No analysis was performed and reported in the study. The authors recommended for unstable angina and non ST elevated MI (NSTEMI) based on the current state of evidence, the combination of aspirin and clopidogrel should be started as soon as possible after the initial presentation if contraindications are not present. This recommendation is supported by the results in the CURE[15] trial that demonstrated that clopidogrel reduced ischemic events irrespective of whether an intervention procedure was used. The authors also recommended that ASA should be continued indefinitely and that clopidogrel should be continued for at least 9 to 12 months and possibly longer, depending on the level of patient's risk.

Hankey and colleagues reported in a Cochrane review[26] and two journal articles[25 36] on four trials involving 22,656 patients. Patients with the diagnoses of a recent MI (n=6302), TIA or ischemic stroke (n=9840), or PAD (n= 6514) were included. Aspirin was compared with ticlopidine in three trials (n=3471 patients) and with clopidogrel in one trial (n=19185 patients). The mean duration of follow-up was about 2 years. The thienopyridines (ticlopidine, clopidogrel) were associated with a nonsignificant reduction in the odds of a MI, 0.88 (95% CI 0.76-1.01) and vascular death, 0.93 (95% CI 0.82-1.06). Clopidogrel or ticlopidine was associated with a modest but statistically significant reduction in the odds of a serious vascular event compared to ASA (12% vs. 13%; OR 0.91, 95% CI 0.84-0.98; p=0.01).

Coronary revascularization via stenting or bypass grafting

- **Head-to-head trials**: (poor/fair quality)

No trials with extended release dipyridamole/ASA in the setting of coronary revascularization) were identified. (Refer to Table 1.)

A total of eight head-to-head trials with the thienopyridines in PCI were identified as eligible. Three studies[37-39] were rated poor in quality. The study conducted by Moussa et al.[38] was an observational nonrandomized comparison between the two agents in a consecutive fashion. The study conducted by Piamsomboon et al.[37] had a small sample size and lacked reporting the method for randomization and allocation concealment, as well as the method for

masking. Juergens et al.[39] also had inadequate allocation concealment, and outcome assessors were not masked in the study. Both studies[37 39] utilized doses of ASA that would no longer be used in clinical practice.

Five randomized head-to-head studies[40-44] of fair quality were included in this review. The study by Atmaca et al.[40] was from a single center and did not describe the method of assessment. In addition, post-randomization exclusions could not be determined. During the 6 day follow-up period, a nonsignficant increased rate in major clinical events (death, acute MI, PCI or bypass surgery) with ticlopidine compared to clopidogrel was observed. The four-week study conducted by Müller et al.[41] was a single-centered, unblinded study and was not powered to show statistical differences in cardiac events. This study was extended to 3 years (median, 28 months) by Mueller et al.[42] In this study,[42] the primary endpoint of cardiovascular mortality was significantly lower in patients assigned to receive ticlopidine compared to those taking clopidogrel, 2.3% vs. 7.3%, (hazard ratio 0.30; p=0.003). The secondary endpoint of the composite of cardiovascular death or nonfatal MI was also significantly lower in patients taking ticlopidine (19/346, 5.5%) compared to those taking clopidogrel, (40/355, 11.3%; p=.005). In addition, all-cause mortality was lower with ticlopidine compared to clopidogrel (hazard ratio 0.30, 95% CI 0.14-0.64; p=0.002). Additional findings regarding the functional status of the enrolled patients based on their responses from questionnaires were not made available. Taniuchi et al.[43] was a randomized, single-center, open-label study and compared clopidogrel and ticlopidine in a broad and unrestricted population. The secondary endpoints in Taniuchi et al.[43] study were the composite rate of thrombocytopenia, major bleeding, cardiac death, Q-wave MI, stent thrombus, and TVR (percutaneous or bypass grafting). Of the cardiac endpoints, cardiac death (1.53% vs. 0.61%, p=0.14) and major adverse clinical events (MACE) (4.60% vs. 3.9%, p=0.55) occurred more frequently in the ticlopidine group but neither reached statistical significance. Additional endpoints occurring more frequently with clopidogrel in the study included acute closure, subacute thrombosis, and TVR, but again these did not reach statistical significance. Di Pasquale et al.[44] conducted a double-blind, randomized, single-center trial comparing ticlopidine 500 mg/day to clopidogrel 75 mg/day in 428 patients hospitalized with an admission diagnosis of first episode of ACS. The diagnosis of ACS included patients with acute or rapidly worsening symptoms thought to be due to coronary artery disease as well as NSTEMI. All patients received ASA 160 mg/day and GP IIb/IIIa infusion. All patients underwent angiography less than 72 hours after admission. Follow-up data was available at 3 and 6 months post PCI. Twenty cases of non-cardiac side effects were observed in the ticlopidine group (4-gastrointestinal, 4-dermatological, 2-major bleeding, 6-minor bleeding, 4- platelet reduction <100,000) compared to 14 in the clopidogrel group (2-dermatological, 2-major bleeding, 6-minor bleeding, 4-platelet reduction <100,000). During the 180 days follow-up, 44 patients from the ticlopidine group showed reocclusions in the PTCA treated vessel vs. 48 patients in the clopidogrel group (p value not significant). The trial was rated fair because the results as presented could not be determined whether they reflected the intent-to-treat population vs. the on-treatment population. In addition, post-randomization exclusions nor drug therapy discontinuation rates could not be determined. Baseline data on platelets nor the corresponding units utilized were not provided. (Details of these trials are included in Evidence Table A1 and Quality Table A2.)

- **Head-to-head trial**: (good quality)

One head-to-head randomized controlled study[14] of good quality called the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) is included. This study randomized patients to one of three arms for 28 days: (1) clopidogrel 300 mg loading dose followed by clopidogrel 75 mg plus ASA 325 mg daily; (2) clopidogrel 75 mg plus ASA 325 mg daily (no loading dose); or (3) ticlopidine 250 mg twice a day plus aspirin 325 mg daily. The CLASSICS[14] trial was primarily a safety study. In CLASSICS, the secondary outcomes were MACE including MI (fatal and non-fatal), target lesion revascularization (TLR), and sudden death. The 30-day rate for MACE was similar between ticlopidine and the combined clopidogrel group. ($p \geq 0.555$).

- **Active-controlled trials**: (poor/fair quality)

The active controlled study performed by Hall et al.[45] was an open-label, randomized, trial comparing ticlopidine and ASA vs. ASA alone after stent implantation; it was judged to be of poor in quality.

Rupprecht et al.[46] randomized patients to one of three groups: (1) ticlopidine; (2) ticlopidine plus ASA 300 mg; or (3) ASA 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 to aspirin or ticlopidine alone. The study randomization was inadequate, allocation was not concealed nor was the outcome assessor masked; the study was rated poor in quality.

Leon et al.[47] studied whether ASA 325 mg plus ticlopidine 250 mg twice a day was as effective as ASA 325 mg alone or ASA plus warfarin (goal International Normalized Ratio (INR) 2.0–2.5) for 4 weeks in preventing stent thrombosis in 1653 patients. The study was randomized, unblinded, and rated fair in quality. The primary endpoint occurrence of stent thrombosis was a hierarchical composite of death from any cause; revascularization of the target lesion without death, evidence of target thrombus of the target vessel on repeated angiography without revascularization, or nonfatal MI in patients who did not undergo repeated angiography. This study showed that aspirin plus ticlopidine was superior to the combination of warfarin and aspirin or aspirin alone in the prevention of stent thrombosis within 30 days after a successful stent procedure.

- **Active-controlled trials**: (good quality)

Three active-controlled trials[15-17] rated to be good in quality were included. The Percutaneous Coronary Intervention Study (PCI-CURE)[15] was a prospectively designed analysis in a subset of patients (n = 2658) from the CURE[12] trial. A PCI was performed at the discretion of the investigator and the use of glycoprotein IIb/IIIa inhibitors was discouraged unless patients developed refractory ischemia or in relation to PCI. Overall, 23.7% of the patients did receive platelet glycoprotein IIb/IIIa inhibitor agents. Fewer patients assigned clopidogrel received intravenous glycoprotein IIb/IIIa inhibitors during PCI than those assigned placebo (26.6% vs. 20.9%; p=0.001). The goal of the study was to assess, in addition to ASA, whether clopidogrel pretreatment was superior to placebo in preventing major ischemic events within the first 30 days after PCI. The benefit from long-term treatment (up to 1 year) with clopidogrel plus aspirin was

also evaluated. Following PCI, approximately 80% of patients received open-label clopidogrel or ticlopidine for a median of 30 days. Thereafter, the blinded study medication was then resumed for the remaining duration of the follow-up period.

The Clopidogrel for the Reduction of Events During Observation (CREDO),[16] a double-blind, randomized, placebo-controlled trial, evaluated the benefit and safety of clopidogrel as adjunct therapy to aspirin over short-term (28 days) and long-term therapy (12 months) in 2116 patients with symptomatic coronary artery disease and objective evidence of ischemia undergoing elective PCI or had a strong likelihood of undergoing PCI between June 1999 to April 2001. The use of glycoprotein IIb/IIIa antagonists was at the discretion at the time of enrollment or given as bail-out during the PCI procedure. Overall, ~45% of all patients received glycoprotein IIb/IIIa agents.[48] The patients (n = 1053) were randomized to a preprocedural loading dose of 300 mg clopidogrel (3–24 hours prior to PCI, mean 9.8 hours) or placebo (n=1063) plus 325 mg ASA daily. The loading dose was administered at 3 to 6 hours in 51% of the patients and at 6 or more hours before PCI in the other patients. After PCI, all the patients received clopidogrel 75 mg and ASA 325 mg daily for 28 days. At that point, the group that received the clopidogrel loading dose continued to receive clopidogrel 75 mg per day, whereas the no-pretreatment group received a matching placebo. The ASA dose after 28 days was in the range of 81 to 325 mg. Drug treatment was completed at 1 year in 63% of patients in the clopidogrel group and 61% of patients in the control group.

The Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty (ARMYDA-2)[17] was a prospective, randomized, double-blind study to evaluate the safety and efficacy of pretreatment with a 600 mg versus a 300 mg loading dose of clopidogrel in improving ischemic complications during coronary intervention. A total of 255 patients scheduled to undergo percutaneous coronary interventions were randomized to a 600 mg (n=126) or 300 mg (n=129) loading dose regimen of clopidogrel 4-8 hours prior to angiography. The patients without contraindications were pretreated before intervention with 100 mg/d of ASA and continued indefinitely. Clopidogrel was continued at a dose of 75 mg/d for 1 month or longer (6 months in patients receiving drug-eluting stents and 9 months in those treated for ACS). Twenty-seven (21%) patients in the 600 mg group and 24 (19%) patients in the 300 mg group received a drug-eluting stent (p=0.68).Timing of the pre-procedural clopidogrel loading dose was similar in both groups. Baseline clinical features between the 2 groups were not significantly different, except for patient age, which was slightly higher (65 ± 10 vs. 63 ± 10) in the 300 mg group, (p=0.027). A glycoprotein IIb/IIIa receptor antagonist was allowed at the operator's discretion and used periprocedurally in both groups, 16 (13%) in the 600 mg group and 17 (13%) in the 300 mg group, (p=0.94). A greater number of patients underwent multivessel intervention in the 600 mg group, (p=0.020). The 30-day primary endpoint was the occurrence of death, MI, or target vessel revascularization (bypass grafting or percutaneous intervention on the original coronary vessel(s).

Mortality: (All-cause and cardiovascular)

In the study conducted by Leon et al.[47] treatment medications (ticlopidine and ASA, ASA, ASA plus warfarin) were started at the end of the PCI procedure. The overall incidence of the primary endpoint (stent thrombosis) in the study was 2.3%. The overall incidence of death within 30 days was 0.06%. In the first 30 days after the stent procedure, death occurred in 3.6%

in the ASA group, 2.7% with ASA plus warfarin and 0.5% in the ASA plus ticlopidine group (p=0.001).

In PCI-CURE,[15] the incidence of cardiovascular death was similar between the two study arms from the time of the PCI to 30 days post-PCI (1.1% for clopidogrel vs. 1.0% for placebo) (RR 1.10, 95% CI 0.52-2.34). Similarly, the incidence of cardiovascular death from the time of the PCI to the end of follow-up (average duration, 8 months) did not differ significantly between the two groups (clopidogrel 2.4%, placebo group 2.3%). (Refer to Table 7.)

In CREDO,[16] death from any cause as a prespecified secondary analysis was not significant at one year for the clopidogrel pretreatment group (18/1053) compared to the no-pretreatment group (24/1063) (1.7 vs. 2.3%; 95% CI 0.41-1.39).

Combined Outcomes (fatal and non-fatal)

In PCI-CURE,[15] the combined endpoints of CV death and MI before and after PCI was 8.8% and 12.6%, favoring the clopidogrel and ASA group compared to the placebo and ASA group (RR 0.69, 95% CI 0.54-0.86; p=0.002). (Refer to Table 7.)

In CREDO,[16] maintaining clopidogrel and ASA for one year resulted in a decrease in the composite primary endpoint (death, MI, or stroke) compared to placebo plus aspirin (8.5% vs. 11.5%; RR 0.73, 95% CI 0.57-0.95, ARR 3%, NNT=33). (Refer to Table 8.)

In ARMYDA-2,[17] the combined endpoints of death, myocardial infarction, or target vessel revascularization (TVR) occurred in 4% of patients in the high loading dose group and 12% of those in the conventional loading dose group at 30 days, (p=0.041). The majority of the difference in the primary endpoint was due to an increased number of periprocedural MIs (defined as a CK-MB increase >3 times above the upper normal limit) that occurred 3 times as often in the 300 mg group compared to the 600 mg group. Twenty patients had MIs by biomarker criteria, 15 in 300 mg clopidogrel group and 5 in 600 mg clopidogrel group. One patient in the 600 mg treatment group had a target vessel revascularization (TVR). No deaths occurred through 30 days.

Cardiovascular events (MI, stroke)

In the Leon et al.[47] study, the decrease in recurrent MI in 30 days, which was an individual component of the composite primary endpoint, was 2.7% with ASA vs. 2.0% with ASA plus warfarin vs. 0.5% with ticlopidine plus ASA (p=0.01).

In PCI-CURE,[15] the incidence of MI within 30 days following PCI was less with clopidogrel plus aspirin (2.1% vs. 3.8%) than placebo plus aspirin (RR 0.56, 95% CI 0.35-0.89, NNT=60). Specifically, a substantive reduction in the incidence of Q-wave MIs was noted with clopidogrel compared to placebo (0.8% to 2.4%, RR 0.35, 95% CI 0.18-0.70, p=0.001, NNT= 65). At 12 months, the RR was lower for the incidence of MI with clopidogrel compared to placebo (4.5% vs. 6.4%, RR 0.71, 95% CI 0.51-0.99, p=0.038, NNT=55). Again, the benefit was primarily driven by the reduction in the incidence of Q-wave MI. Overall, the combined endpoints of CV death and MI before and after PCI was 8.8% and 12.6%, favoring the clopidogrel and ASA group compared to the placebo and ASA group (RR 0.69, 95% CI 0.54-

0.86, p=0.002). (Refer to Table 7.) Stroke was not an outcome evaluated in the PCI-CURE trial.

Table 7. PCI-CURE:[15] Major Outcomes Events

	Clopidogrel + ASA n= 1313		Placebo + ASA n=1345		RR (95% CI)* p value*	NNT
	PCI-30 days n (%)	PCI to end of f/u n (%)	PCI-30 days n (%)	PCI to end of f/u n (%)		
CV Death, MI	38 (2.9)	79 (6.0)	59 (4.4)	108 (8.0)	0.83 (0.70-0.99) 0.047	29
CV Death	14 (1.1)	32 (2.4)	13 (1.0)	31 (2.3)	1.07 (0.65-1.75) NS	NS
MI	28 (2.1)	59 (4.5)	51 (3.8)	85 (6.4)	0.71 (0.51-0.99) 0.038	55
Q-wave MI	11 (0.8)	20 (1.5)	32 (2.4)	47 (3.5)	0.43 (0.26-0.73) 0.001	51
Overall results; events before and after PCI						
CV Death, MI	116 (8.8)		169 (12.6)		0.69 (0.54-0.87)** 0.002**	27

CV= cardiovascular; f/u= follow-up; RR= relative risk; MI= myocardial infarction. * Calculated for clopidogrel + ASA vs. placebo + ASA at time of PCI to end of follow-up. ** Calculated at time before PCI to end of follow-up. NNT=Number Needed to Treat; NS = Not Significant; NNT=Number Needed to Treat; PCI=percutaneous coronary intervention; ASA=aspirin; CI=confidence interval.

A post-hoc analysis[48] from the CREDO trial examined the optimal timing of administering a clopidogrel loading dose in terms of ischemic complications at 28 days. More specifically, 1,762 patients undergoing PCI were randomized to 300 mg clopidogrel or matching placebo 3-24 hours (mean, 9.8 hours) prior to PCI. Both groups were treated with clopidogrel 75 mg and aspirin 325 mg daily for 28 days after the PCI. For patients randomized to placebo, no relationship between the duration of pre-treatment study drug treatment before PCI and the occurrence of the primary 28-day combined endpoint of death, MI, or UTVR was seen. However, in those patients that were randomized to receive a 300 mg loading dose of clopidogrel, a strong relationship between the duration of pre-treatment and outcome was seen starting after 10-12 hours of pre-treatment and this difference became statistically significant after 15 hours of pre-treatment, (RRR 58.8%; p=0.028) and was seen even as far as 24 hours pre-treatment prior to PCI. No significant differences in patient baseline or procedural characteristics were noted except that those patients pretreated with clopidogrel ≥15 hours before PCI received less GP IIb/IIIa agents compared to those patients that were pre-treated <15 hours. Patients receiving 300 mg clopidogrel loading dose up to 10 hours before the PCI had identical outcomes as did those patients who received only 75 mg at the time of the PCI. The authors concluded that if pre-treatment with clopidogrel 300mg loading dose is to be of any benefit before PCI, it should be initiated at least 15 to 24 hours beforehand. Otherwise, little benefit is obtained compared with 75 mg of clopidogrel at the time of the PCI when treatment duration is <~12 hours before the procedure with clopidogrel 300 mg loading dose. No significant differences in the incidence of major and minor bleeding at 28 days were observed between those patients that received pretreatment clopidogrel loading dose <15 hours or ≥ 15 hours prior to PCI.

In ARMYDA-2[17] study, a multivariable analysis identified a 50% risk reduction of periprocedural MI with pretreatment 600 mg loading dose of clopidogrel (OR 0.48, 95% CI

0.15-0.97; p=0.044). The sample size calculation was based on post-PCI increases in CK-MB levels, and not the primary endpoint. A further reduction in the risk of MI was found in those patients randomized to clopidogrel 600 mg loading dose also receiving a statin prior to PCI (OR 0.20, 95% CI 0.10-0.74; p=0.017).

The primary endpoint in the observational study conducted by Hochholzer et al[49] was evaluating platelet aggregation. Studies evaluating the time dependence of platelet inhibition following a loading dose of clopidogrel were not an outcome of interest for this paper. Although this observational study was not designed to investigate the relation between clinical outcomes and timing of PCI following clopidogrel 600 mg loading dose, nevertheless, the 30-day rate of major adverse cardiac events (MACE) after PCI and noncardiac complications until discharge was reported. Death, nonfatal MI (defined as nonfatal MI with new Q wave or rise in creatinine kinase to 3 times the upper limit of normal with concomitant rise in MB isoenzyme) and target vessel revascularization (TVR) events were also reported. The study evaluated 1001 consecutive patients scheduled for cardiac catherization as potential candidates for PCI and was taking ASA ≥ 100 mg/d. Patients with a diagnosis of an acute MI or on chronic oral anticoagulation were not included. Among the 428 patients undergoing PCI, the 30-day composite rate of MACE was 1.9%. No significant difference in the incidence of 30 day rate of nonfatal MI in patients undergoing PCI < 2 hours following clopidogrel loading dose vs. those patients undergoing PCI ≥ 2 hours was seen (p=0.49). No significant difference with respect to the incidence of MACE, death, TVR, TIMI major bleed (intracranial hemorrhage or drop in hemoglobin of >5 g/dL) or transfusion between the patients undergoing PCI within 2 hours after clopidogrel 600 mg loading dose compared to those patients undergoing PCI ≥ 2 hours after the clopidogrel loading dose was observed. Although more studies need to be conducted, the high loading dose of clopidogrel used in this observational platelet inhibition study was well tolerated and was not associated with an excessive risk of bleeding complications but did not impact any of the reported clinical outcomes.

Invasive vascular procedure failure (including need for additional invasive vascular procedures)

In the Leon et al.[47] study, revascularization of the target lesion at 30 days, which was an individual component of the composite primary endpoint, was 3.4% with ASA vs. 2.5% with ASA plus warfarin vs. 0.5% with ticlopidine plus ASA (p=0.002). Percutaneous transluminal coronary angioplasty (PTCA) occurred in 3.1%, 2.5%, and 0.5% with ASA, ASA plus warfarin, and ASA plus ticlopidine respectively (p=0.003).

In PCI-CURE,[15] urgent revascularization (second PCI or any coronary artery bypass graft procedure on a non-elective basis) was decreased at 30 days, but not significantly so, with clopidogrel compared to placebo (2.8% vs. 1.9%; RR 0.67, 95% CI 0.41-1.11). However, when rates of nonfatal MI, urgent-target-vessel revascularization (UTVR), and CV death were combined in the same time period, events were statistically lower in the clopidogrel group compared to placebo (4.5% vs. 6.4%; RR 0.70, 95% CI 0.50-0.97; p=0.03, NNT=53). Any revascularization from the time of the PCI to the end of follow-up remained lower with clopidogrel than placebo (14.2% vs. 17.1%), but the results were only nominally significant (RR 0.82, 95% CI 0.68-1.00; p= 0.037). The rates for combined CV death, MI, or any revascularization from PCI favored clopidogrel over placebo at 12 months (18.3% vs. 21.7%; RR 0.83, 95% CI 0.70-0.99, p=0.03).

In CREDO,[16] among patients undergoing PCI, pretreatment with clopidogrel loading dose had a non-significant 18.5% relative reduction in the combined endpoint of death, MI, or UTVR at 28 days (6.8% pretreatment vs. 8.3% no pretreatment); RR 18.5 (95% CI 14.2 - 41.8; p=0.23). A prespecified secondary analysis included the individual components of the composite primary endpoint, the time clopidogrel was administered (< 6 hours vs. ≥ 6 hours) and the need for revascularization or any revascularization at 1 year. When the pre-protocol population was analyzed based on the prespecified time-to-treatment intervals of 3 to 6 hours, 6 to 12 hours, and 12 to 24 hours prior to PCI, patients who had received clopidogrel at least 6 hours prior to PCI had a relative reduction of 38.6% (95% CI -1.6% - 62.9%; p=0.051) for this endpoint at 28 days compared to no reduction at all when clopidogrel was given less than 6 hours prior to PCI.

Table 8. CREDO[16]: Major outcome events at 1 year

	Clopidogrel + ASA n= 1053 n (%)	Placebo + ASA n=1063 n (%)	RR (95% CI)* p value*	NNT*
Death, MI, stroke	89 (8.5)	122 (11.5)	0.73 (0.57-0.95) 0.021	3.0
Death, MI	84 (8.0)	111 (10.4)	0.76 (0.58-1.00) 0.051	2.4
Death	18 (1.7)	24 (2.3)	0.76 (0.41-1.39) NS	NS
MI	70 (6.6)	90 (8.5)	0.79 (0.58-1.06) NS	NS
Stroke	9 (0.9)	12. (1.1)	0.76 (0.32- 1.79) NS	NS
Revascularization				
Any TVR	139 (13.2)	144 (13.5)	0.97 (0.78-1.21) NS	NS
Urgent TVR	21 (2.0)	23 (2.2)	0.92 (0.51-1.66) NS	NS
Any revascularization	225 (21.4)	223 (21.0)	1.01 (0.86-1.20) NS	NS

RR= relative risk; NNT=Number Needed to Treat; MI= myocardial infarction; TVR= target vessel revascularization.
* Calculated for clopidogrel + ASA vs. placebo + ASA at 1 year. NS = Not Significant.

Systematic Review:

Two meta-analyses[28 29] comparing the combination of ASA with clopidogrel to ASA and ticlopidine were identified. The first analysis, conducted by Bhatt et al.[29] included three randomized trials[14 41 43] and seven single-center registries of which three[38 50 51] were evaluated for this drug class review. (Details of these trials are included in Evidence Table A1 and Quality Table A2.) All the randomized trials differed in their inclusion and exclusion criteria as well as the interventions implemented. The definitions of the MACE components—namely MI, TVR, and sub-acute stent thrombosis (SAST)—differed. However, all-cause mortality was the consistent and prespecified endpoint common to all these trials. A statistically significant odds reduction in all-cause mortality of 56% with clopidogrel plus aspirin versus ticlopidine plus aspirin was seen (0.48% vs. 1.09%, p= 0.001). When the analysis was limited to the three randomized trials, thereby eliminating the registries, the odds ratio was similar but not statistically significant for the combination of clopidogrel plus ASA (OR 0.47, 95% CI 0.17-1.30; p=0.14).

The second meta-analysis, done by Casella et al.[28] included the same three randomized trials[14 41 43] and six of the seven registries, of which three[38 50 51] were evaluated in this review. (Details of these trials are included in Evidence Table A1 and Quality Table A2.) The prespecified primary endpoint was the combined death and non-fatal MI at 30 days. A significant OR favoring clopidogrel plus ASA was seen for the primary endpoint (OR 0.63, 95% CI 0.47-0.85; p=0.003). When the analysis was limited to the three randomized clinical trials, the primary endpoint for ASA plus clopidogrel (1.2%, n=19/1529) was similar to ASA plus ticlopidine (1.2%, n=15/1207) (OR 1.05, 95% CI 0.52-2.12; p=0.9). No significant difference in mortality for patients treated with clopidogrel plus aspirin (0.4%, n=6/1529) compared to ticlopidine plus aspirin (0.7%, n= 9/1207) (OR 0.60, 95% CI 0.21-1.70; p=0.3).

A meta-analysis conducted by Bionid-zoccai et al.[52] compared the incidence of all-cause mortality after coronary stenting in patients treated with clopidogrel (with and without loading dose) and ticlopidine. The secondary end-point was the combined rate of death or non-fatal myocardial infarction. Other adjudicated events were MI, stroke, repeat revascularization or clinical restenosis, major bleeding, and severe hematological adverse effects. The meta-analysis included five randomized trials[14 37 40 42 43] all of which are evaluated in the current review. (Details of these trials are included in Evidence Table A1 and Quality Table A2.) A total of 2,962 patients were randomized with an average follow-up of 7.4 months. Clopidogrel loading dose was administered in three of the studies; absent in one study; and included in one of the three study arms in one study. Similar rates for the overall risk of death or MI were observed between clopidogrel and ticlopidine. Similar rates between the two medications were observed for rates of clinical revascularization and non-cardiac safety profiles. A significant difference was seen when clopidogrel therapy was used in the absence of any loading dose. Clopidogrel without a loading dose was associated with a 3-fold increased risk of death compared to ticlopidine (4.2% vs. 1.7%; RR 2.9, 95% CI 1.45-6.1; p=0.0029). Likewise, clopidogrel without a loading dose yielded a higher risk of death or MI compared to ticlopidine, 6.4% vs. 4.1%; RR 1.89, 95% CI 1.15-3.1; p=0.012, respectively. This meta-analysis had several limitations including small number of studies of different quality, small number of overall events as well as varying degrees of glycoprotein IIb/IIIa inhibitors utilized (0-48%). The standard of practice now recommends a loading dose of clopidogrel so these findings are of interest but are not of practical importance.

A meta-analysis conducted by Purkayastha et al[53] assessed the effect of clopidogrel on postoperative outcome after coronary surgery by comparing patients who were taking clopidogrel at the time of surgery with patients who stopped clopidogrel at least seven days before surgery. However, this meta-analysis had several methodological limitations including combining retrospective and prospective studies with inadequate description and citations of studies used in the analysis. Moreover, patients' characteristics were not described (including whether other antiplatelet agents were being taken concurrently). Due to these obvious limitations, no conclusions from this analysis can be made.

In the systematic review by Tran et al.[35] the recommendations that ASA should be continued indefinitely and clopidogrel continued approximately 12 months, and possibly longer depending on the patients' risk, were based on the results of the PCI-CURE[15] and CREDO[16] trials.

(More details of these meta-analyses are included in Table A3–Systematic Reviews.)

Key Question 1b. Outcomes: Prior Ischemic Stoke or TIA

In patients with prior ischemic stroke or TIA, what is the comparative efficacy of the newer antiplatelet agents in mortality (all-cause and cardiovascular), cardiovascular events (MI, stroke), and invasive vascular procedure failure (including the need for additional invasive vascular procedures)?

Overall Summary of Evidence for comparative effectiveness and safety of the newer antiplatelet agents in patients with ischemic stroke or TIA

Efficacy Trials:

- No head-to-head trials are available; therefore no comparative conclusions can be made between these newer antiplatelet agents in the setting of stroke or TIA.
- Active-controlled trials: Five multicenter randomized controlled trials (RCTs) were included.

ERDP/ASA: The Second European Stroke Prevention Study[18] (ESPS-2) consisted of four treatment arms: (1) extended release dipyridamole (ERDP) 200 mg; (2) extended-release dipyridamole 200 mg and immediate release ASA 25 mg (ERDP/ASA); (3) immediate-release ASA 25 mg; (4) placebo. The study had two primary efficacy endpoints: stroke (fatal or non-fatal), and death from all causes. In ESPS-2,[18] ERDP did not show a statistically significant reduction in any of the primary outcomes compared with aspirin. Compared with placebo, the ERDP/ASA combination was twice as effective for preventing stroke as either aspirin or extended release dipyridamole alone. ERDP/ASA was significantly more effective than aspirin alone in patients with stroke or TIAs in reducing the outcome of stroke. ERDP/ASA was favored for the outcome of stroke and/or death compared to aspirin although the CI's upper limit equaled one which raises the possibility that ERDP/ASA may not be more effective or perhaps only marginally more effective at reducing stroke and/or death than aspirin alone. ERDP/ASA did not significantly reduce the outcome of death compared with aspirin alone.

Primary Outcomes:[34] ERDP/ASA vs. ASA at 24 months is depicted

- Stroke (fatal and non-fatal): 9.5% vs. 12.5%; RR 0.76, 95% CI 0.64-0.93; p=0.006
- Stroke and/or death: 17.3% vs. 20.0%; RR 0.87, 95% CI 0.74-1.0; p=0.056
- Death from all causes: 11.2% vs. 11.0%; RR 1.02, 95% CI 0.84-1.23; p=0.942

As noted below, a number of secondary outcomes were reported. ERDP was not beneficial compared with aspirin for any of the secondary outcomes. ERDP/ASA was significantly more effective than aspirin at reducing stroke or TIA, other vascular events (OVEs), ischemic events (fatal and non-fatal) and vascular events. The point-estimate favored ERDP/ASA for the other outcomes reported but the findings were not statistically significant. Although MI was a secondary endpoint, ESPS-2 was not designed to study the effect of the different treatments on the prevention of MI. Indeed, the number of MIs were too low to discern whether a trend existed for one drug or another.

Secondary Outcomes:[34] ERDP/ASA vs. ASA at 24 months is depicted

- TIAs: 10.4% vs. 12.5%; RR 0.83, 95% CI 0.69-1.01
- Stroke or TIA: 18.1% vs. 22.6%; RR 0.80, 95% CI 0.70 - 0.92
- MIs: 2.1% vs. 2.4%; RR 0.90, 95% CI 0.57 - 1.41
- Other Vascular Events (deep venous thrombosis, pulmonary embolism, peripheral arterial occlusion, venous retinal vascular events): 1.3% vs. 2.3%; RR 0.55, 95% CI 0.33 - 0.94
- Ischemic events (fatal or non-fatal) stroke, MI or sudden death): 12.5% vs. 16.1%; RR 0.77, 95% CI 0.65 - 0.92
- Vascular deaths: (fatal stroke, fatal MI, death due to other vascular events or cardiac failure, sudden deaths of unknown cause, and hemorrhagic deaths (non-cerebral fatal bleeding) 7.1% vs. 7.2%; RR 0.99, 95% CI 0.77 - 1.27
- Vascular events (vascular death, non-fatal stroke, non-fatal MI and non-fatal OVE: 14.9% vs. 19.0%; RR 0.78, 95% CI 0.67 - 0.91

The European/Australasian Stroke Prevention in Reversible Ischemia Trial[21] (ESPRIT) was a randomized, controlled, non-blinded international study evaluating patients taking aspirin (median dose 75 mg; range, 30-325 mg) with (n=1363) or without (n=1376) 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 ASA/ERDP dosage form. Twenty-four patients from one 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. In that regard, the intention-to-treat analysis was similar to the on-treatment analysis. The study results indicate that the combination therapy of aspirin and ERDP is more effective than aspirin alone in the prevention of new serious vascular events in patients after a non-disabling cerebral ischemic stroke of presumed arterial origin. Patients taking the combination therapy had fewer major bleeding complications than patients allocated to aspirin alone, although this was not significant. The major limitation of this study was that it was non-blinded, although the outcomes were determined by the auditing committee who were unaware of allocated study treatment.

Primary Outcomes: ERDP/ASA vs. ASA (intent-to-treat)

- First occurrence of the composite death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication: 12.7% vs. 15.7%; RR 0.81, 95% CI 0.67-0.97

Numerous secondary outcomes were evaluated in the ESPRIT[21] trial. Patients taking the combination of extended-release dipyridamole and aspirin had a lower incidence of death from all vascular causes and the combined outcome of death from all vascular causes and non-fatal stroke compared to aspirin monotherapy. The trend favored ERDP plus ASA for all the other outcomes, although the CI crossed over 1.

Secondary Outcomes: ERDP/ASA vs. ASA (intent-to-treat)

- Death from all causes: 6.8% vs. 7.8%; RR 0.88, 95% CI 0.67-1.15
- Death from all vascular causes: 3.2% vs. 4.4%; RR 0.74, 95% CI 0.51-1.08

- Death from all vascular causes and non-fatal stroke: 9.7% vs. 12.4%; RR 0.78, 95% CI 0.63-0.97
- All major ischemic events: (non-hemorrhagic death from vascular causes, non-fatal ischemic stroke, or non-fatal MI):10.3% vs. 12.6%; RR 0.81, 95% CI 0.65-1.00
- All vascular events: (death from vascular causes, non-fatal stroke, or non-fatal MI) 10.9% vs. 14.0%; RR 0.78, 95% CI 0.64-0.96
- Major bleeding complications: 2.6% vs. 3.9%; RR 0.67, 95% CI 0.44-1.01

Clopidogrel: The MATCH[19] trial was a randomized, double-blind, international study evaluating the risk of recurrent ischemic vascular events. The study included 7599 high-risk patients who were randomized to receive clopidogrel plus placebo or clopidogrel plus 75 mg aspirin with a follow-up of 18 months for each patient. The primary composite endpoint was ischemic stroke, MI, vascular death, or rehospitalization for an acute ischemic event (including angina pectoris, worsening of PAD requiring therapeutic intervention or urgent revascularization, and TIA). The study demonstrated that the combination of clopidogrel 75 mg plus aspirin was no more effective than clopidogrel alone in reducing major vascular events in high-risk patients who had recently suffered an ischemic stroke or TIA. That combination, however, increased the risk of life-threatening and major bleeding compared to clopidogrel by itself.

Primary Outcome: ASA + clopidogrel vs. placebo + clopidogrel

- First occurrence of composite of ischemic stroke, MI, vascular death (including hemorrhagic death) or rehospitalization of an acute ischemic event (including unstable angina pectoris, worsening of peripheral arterial disease requiring therapeutic intervention or urgent revascularization, or TIA): 15.7% vs.16.7%; RR 0.94, 95% CI 0.85-1.04

Numerous secondary outcomes were evaluated including individual and various combinations of each of the components of the primary endpoint, including death from any cause and both types of strokes. The combination of aspirin and clopidogrel did not significantly reduce any of the secondary outcomes.

Secondary Outcomes: ASA + clopidogrel vs. placebo + clopidogrel

- MI, ischemic stroke and vascular death: 11.7% vs. 12.4%; RR 0.94, 95% CI 0.83-1.06
- MI (fatal or not): 1.9% vs. 1.8%; RR 1.07 95% CI 0.77-1.49
- Ischemic stroke (fatal or not): 8.1% vs. 8.8%; RR 0.93, 95% CI 0.80-1.08
- Vascular death: 3.3% vs. 3.2%; RR 1.03, 95% CI 0.80-1.31
- Ischemic stroke (fatal or not) and vascular death: 10.6% vs. 11.3%; RR 0.93, 95% CI 0.82-1.06
- Any stroke: ischemic stroke, primary intracranial hemorrhage or non-classifiable stroke (fatal or not): 8.9% vs. 9.1%; RR 0.98, 95% CI 0.85-1.13
- Death (all cause): 5.3% vs. 5.3%; RR 1.00, 95% CI 0.83-1.21
- Non-fatal MI, non-fatal ischemic stroke, rehospitalization for acute ischemic event: 13.2% vs.14.4%; RR 0.93, 95% CI 0.83-1.04

Ticlopidine: The TASS[20] study was a North American randomized, double-blind study comparing the effect of ticlopidine 250 mg twice a day to ASA 650 mg twice a day with a mean

40-month follow-up. In TASS,[20] ticlopidine was somewhat more effective than ASA 650 mg in reducing the risk of death from any cause or the risk of nonfatal stroke (primary endpoint) in patients with a history of recent TIA or minor stroke, p=0.048.

Primary Outcome: ticlopidine vs. ASA

- Composite of non-fatal stroke or death from all causes: 20% vs. 22.7%; RR 0.88, 95% CI 0.77 – 1.01

The cumulative event-rate curves for the incidence of stroke (non-fatal or fatal) was statistically significant between ticlopidine and aspirin at 5 years, (p=0.024). However, the CI barely crossed one which raised the possibility that the two medications may be similar for this endpoint.

Secondary Outcome: ticlopidine vs. ASA
Composite of fatal and nonfatal stroke: 11.2% vs. 13.8%; RR 0.84, 95% CI 0.69-1.01

Gorelick et al.[54] conducted a randomized, double-blind multicenter study comparing ticlopidine and ASA for 2 years in African-Americans patients with a history of stroke (n=1809, age 29–85).

Primary Outcome: ticlopidine vs. ASA

- Composite of recurrent stroke, MI, or vascular death: 14.7% vs. 12.3%; HR1.22, 95% CI 0.94-1.57

Secondary Outcome: ticlopidine vs. ASA

- Any recurrent stroke (fatal or nonfatal): 11.9% vs. 9.5%; HR 1.28 95% CI 0.96-1.72

Overall, among all the RCTs with long duration in patients with ischemic stroke or TIA, only ERDP/ASA demonstrated a significant reduction in the incidence of all stroke, non fatal strokes and stroke or TIA combined. No difference was seen with clopidogrel in ischemic stroke at 18 months in the MATCH[19] trial. All the newer antiplatelet agents resulted in no difference in all-cause/CV mortality.

Meta-analyses: Five meta-analyses[21 25 26 36 55]were evaluated. Three of the meta-analyses[25 26 36] demonstrated that in high risk vascular patients, the risk of stroke (any type) decreased in the thienopyridine group compared to the aspirin group. One meta-analysis[55] reported a 25% reduction in non-fatal stroke when ESPS-2 results were added to the CV trials from the 1994 Antiplatelet Trialists' Collaboration (ATC).[56] Of interest, the authors of the ESPRIT[21] trial performed a meta-analysis adding their results to that of ESPS-2[18] trial as well as to 4 other trials conducted prior to ESPS-2. A total of 3,888 patients were allocated to aspirin and dipyridamole and 3,097 to aspirin alone. The overall risk ratio favoring aspirin plus dipyridamole compared to aspirin alone for patients with cerebral ischemia of presumed arterial origin for the composite outcome of vascular death, non-fatal stroke, or non-fatal myocardial infarction was 0.82 (95% CI 0.74-0.91). The respective RR for that endpoint for ESPS-2[18] was 0.78 (95% CI 0.67-0.91) compared to RR 0.78 (95% CI 0.64-0.96) for the ESPRIT[21] trial. The authors suggest that the results from the ESPRIT trial are consistent with that of ESPS-2; that is, there is more benefit

with respect to the occurrence of all vascular event with the combination therapy of ERDP plus aspirin compared to aspirin monotherapy.

The overall grade of evidence is good.

Safety/Adverse Events:

No head-to-head trials are available.

Overall, neutropenia may occur with ticlopidine in up to 2.4% of patients, with 0.85% of these having severe neutropenia or agranulocytosis. As a reference point, this would be slightly less than the incidence of agranulocytosis with clozapine (estimated incidence, 1–2%). The incidence of neutropenia with clopidogrel is similar to that with aspirin.

In the ESPS-2[57] trial, the adverse event rate was high in all the study arms, including with placebo. Overall, adverse effects (one or more) occurred in 79.7%, 78.9%, 80.2% and 70.1% patients taking ERDP/ASA, ERDP, ASA, and placebo, respectively. Headache, dizziness, and GI symptoms were the most frequent adverse events reported for ERDP/ASA. Headache occurred significantly more often in patients taking ERDP alone or ERDP in combination with aspirin. Diarrhea occurred more frequently in patients treated with ERDP alone or ERDP with aspirin compared to aspirin alone or to placebo ($p<0.001$). The incidence of bleeding events (any site) was nearly twice as high in both aspirin groups compared to ERDP or placebo. The frequency of bleeding complications was similar in the ERDP/ASA group and the aspirin group. Compared with ERDP, the incidence of any bleeding complications, including mild, moderate and severe, was significantly higher in the ERDP/ASA group. There was no difference in the incidence of other adverse events, such as GI event and headache, between the two groups.

ERDP/ASA vs. ASA:

- Any adverse event: 64% vs. 60.0%; RR 1.07, 95% CI 1.01 -1.08
- Bleeding complications (any site): 8.7% vs. 8.2; RR 10.7, 95% CI 0.85-1.33
- Mild bleeding: 5.1% vs. 5.0%; RR 1.02, 95% 0.76-1.38
- Moderate bleeding: 2.0% vs. 2.0%; RR 1.00, 0.62-1.61
- Severe or fatal: 1.6% vs. 1.2%; RR 1.35, 0.76 – 2.40
- Headache: 38.2% vs. 33.1%; RR 1.15, 95% CI 1.05-1.26
- Gastrointestinal event: 32.8% vs. 30.4%; RR 1.08, 95% CI 0.97-1.19
- Dizziness: 29.5% vs. 29.2%; RR 1.01, 95% CI 0.91-1.12

In ESPRIT[21] trial, 34% of the patients discontinued the combination therapy due to side-effects, mainly headache (26%). Of the patients that were allocated to aspirin monotherapy, 13% discontinued therapy, mainly of a medical reason, such as a new TIA or stroke or an indication for oral anticoagulant therapy.

ERDP/ASA vs. ASA

- Major bleeding: 2.6% vs. 3.9%; RR 0.67, 95% CI 0.44-1.01
- Minor bleeding: 12.5% vs. 12.2%; RR 1.03, 95% CI 0.84-1.25

In MATCH[19] trial, adding aspirin to clopidogrel increased the risk of life-threatening or major bleeding compared to clopidogrel alone.

clopidogrel + ASA vs. clopidogrel

- Life-threatening bleeding: 2.6% vs. 1.3%; RR 1.97, 95% CI 1.40-2.77; p<0.0001
- Fatal-bleeding: <0.4% vs. <0.3%; RR 1.46, 95% CI 0.68-3.15;p=0.328
- Non-fatal bleeding: 2.2% vs. 1.0%; RR 2.14, 95% CI 1.46-3.14; p<0.001
- Major bleeding: 1.9% vs. 0.6%; RR 3.34, 95% CI 2.08-5.36 p<0.0001
- Minor bleeding: 3.2% vs. 1.0%; RR 3.09 95% CI 2.16-4.43 p<0.0001

In TASS,[11] discontinuation of the therapy due to adverse effects (primarily diarrhea and rash) occurred more with ticlopidine than aspirin. Patients more often prematurely terminated ticlopidine than aspirin (51.6% vs. 47%, p<0.05).

ticlopidine vs. ASA

- Severe neutropenia: 0.9% vs. 0.0%; RR Not calculated
- Diarrhea: 20.4% vs. 9.8%; RR 2.08, 95% CI 1.73-2.49
- Gastrointestinal pain: 7.2% vs. 10.0%; RR 0.72, 95% CI 0.57-0.91
- Gastrointestinal hemorrhage: 0.5% vs. 1.4%; RR 0.34, 95% CI 0.14-0.79
- Gastritis: 0.9% vs. 1.7%; RR 0.50, 95% CI 0.26-0.98
- Rash: 11.9% vs. 5.2%; RR 2.26, 95% CI 1.76-2.92

Subgroups:

No conclusion about the comparative effectiveness or safety of the newer antiplatelet agents based on age, gender, race, comorbidities or other medications can be made from this body of evidence in patients with CVA or TIA.

- **Head-to-head trials**: No relevant head-to-head trials were identified. Several key trials have compared a newer antiplatelet agent with aspirin, as discussed below.

- **Active-controlled trials**: (poor/fair quality)

The study conducted by Ito et al.[58] compared the efficacy and safety of two regimens of ticlopidine with and without ASA. The study was judged of poor quality for the following reasons: the method of randomization and the outcome assessors were unknown, allocation concealment was not reported, and the status of blinding of providers/patients could not be determined.

ESPRIT[21] (European/Australasian Stroke Prevention in Reversible Ischemia Trial) was a randomized, open, unblinded, controlled, multicenter study comparing dipyridamole and aspirin to aspirin alone in patients with a transient ischemic attack or a minor ischemic stroke of presumed arterial origin. Patients were followed for 3.5 years. Dipyridamole 200 mg twice a day, either as a fixed combination with aspirin (25 mg) or as a free combination (aspirin and ERDP prescribed as separate agents) was administered. The median aspirin dose was 75 mg (range, 30 mg - 325 mg) in the free combination group as was the case for patients that received aspirin

alone. Of the patients randomized to the combination of dipyridamole and aspirin, 83% (n=1131) used the extended-release dipyridamole (ERDP) dosage form as a separate component, whereas 8% of patients used the combination of ASA/ERDP (Aggrenox®). The primary outcome was the first occurrence of the composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication. Secondary outcome events included death from all causes, death from all vascular causes, death from all vascular causes and non-fatal stroke, all major ischemic events (non-hemorrhagic death from vascular causes, non-fatal ischemic stroke, or non-fatal myocardial infarction), all vascular events (death from vascular causes, non-fatal stroke, or non-fatal myocardial infarction), and major bleeding complications including all intracranial bleeding, any fatal bleeding, or any bleeding requiring hospital admission.

- **Active-controlled trials**: (good quality)

Gorelick et al.[54] conducted a randomized, double-blind multicenter study comparing ticlopidine and aspirin for 2 years in African-Americans patients with a history of stroke (n=1809, age 29–85). The composite primary endpoint was recurrent stroke, MI, or vascular death. The secondary outcome was fatal or nonfatal stroke. The blinded phase of the study was discontinued after 6.5 years due to low probability that ticlopidine would prove superior to aspirin. Neither the composite endpoint nor any of the individual outcomes was significant during a two-year follow-up. A high drop rate was seen in this study; 15.2% in the ticlopidine group vs. 13.3% in the aspirin group. The study was judged to be fair-good in quality.

The Second European Stroke Prevention Study (ESPS-2)[18 57] consisted of four treatment arms: (1) extended release dipyridamole (ERDP) 200 mg (n=1650); (2) extended-release dipyridamole 200 mg and immediate-release ASA 25 mg (ERDP/ASA) (n= 1650); (3) immediate-release ASA 25 mg (n=1649); (4) placebo (n=1649). The study had two primary efficacy endpoints: stroke (fatal or non-fatal) and death from all causes. Additionally, four secondary efficacy endpoints were evaluated (1) MI; (2) other vascular events (including pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, or retinal vascular accident); (3) TIAs; and (4) ischemic events (including MI, stroke, and sudden death of thrombotic origin).

The Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attack or Recent Ischemic Stroke (MATCH)[19] study was a randomized, double-blind, international study evaluating the risk of recurrent ischemic vascular events with clopidogrel plus placebo or clopidogrel plus 75 mg aspirin. The study included 7599 high-risk patients for recurrent vascular events and had 18 months follow-up for each patient. Enrolled patients had either a history of a previous ischemic stroke (IS) (78.9%) or TIA (21.1%) within 3 months prior to randomization and one additional vascular risk factor (e.g., previous IS, previous MI, history of angina pectoris, symptomatic PAD, or history of diabetes mellitus) within the preceding 3 years. The primary composite endpoint was IS, MI, vascular death or rehospitalization for an acute ischemic event (including angina pectoris, worsening of PAD requiring therapeutic intervention or urgent revascularization, and TIA).

The Ticlopidine Aspirin Stroke Study (TASS)[20] was a randomized, double-blind study, conducted in North America, comparing the effect of ticlopidine 250 mg twice a day to ASA 650 mg twice a day, with a mean 40-month follow-up. The primary endpoint was the composite of non-fatal stroke or death from all causes.

(More details of these studies are included in Evidence Table A1 and Quality Table A2.)

Mortality: (All-cause and cardiovascular)

Gorelick et al.[54] reported no difference in the all cause mortality and fatal or non-fatal MI with ticlopidine compared with ASA at two years.

In ESPS-2,[18 59] none of the treatment arms showed a significant reduction in the mortality risk (primary endpoint) by 2 years: ERDP, 11.4% (188/1654); ERDP/ASA, 11.2% (18/1650); ASA, 11.0% (182/1649); placebo, 12.2% (202/1659) (RR 1.01, 95% CI 0.84-1.23). A beneficial trend was seen when ERDP/ASA was compared to ERDP monotherapy but was not seen when ERDP/ASA was compared with ASA monotherapy.

In MATCH,[19] death from any cause (a secondary endpoint) was similar between clopidogrel plus ASA and clopidogrel alone. (Refer to Table11 for other outcomes.)

In TASS,[20] death from all causes (first or any subsequent event) was 11.4% (175/1529) with ticlopidine and 12.7% (196/1540) with ASA at five years (RR 0.90, 95% CI 0.74-1.08). The primary endpoint, non-fatal stroke or death from any cause occurred in 20% and 22.7% with ticlopidine and ASA respectively (RR 0.88, 95% CI 0.77-1.01, p=0.048). The benefit of ticlopidine was apparent early during the first year of therapy and persisted during the entire five years of follow-up.

In ESPRIT,[21] the RR for death from all causes between the aspirin plus dipyridamole compared to aspirin alone group was 0.88 (95% CI 0.67-1.15) in the intention-to- treat analysis. Death from all vascular causes and death from all vascular causes, non-fatal stroke (whichever event occurred first) between the combination group compared to aspirin alone was RR 0.74 (95% CI 0.51-1.08) and RR 0.78 (95% CI 0.63 to 0.97), respectively.

Combined Outcomes (fatal and non-fatal)

In ESPS-2,[59] the combined endpoint of stroke and/or death, the risk reduction with ASA alone vs. placebo was 13.2%; p=0.016 and with extended-release dipyridamole alone vs. placebo was 15.4%; p=0.015. The pair-wise comparison between the combination therapy vs. placebo was 24.4%; p<0.001. The pair-wise comparisons were not significantly different for the endpoint of stroke and/or death between ERDP/ASA vs. ASA; p=0.06 or ERDP/ASA vs. ERDP monotherapy; p=0.07. (See Tables 9 and 10.)

In ESPRIT,[21] in the intention-to-treat analysis, 13% (173/1363) of the patients assigned to combination therapy had at least one primary outcome event (first occurrence of the composite death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complications) vs. 16% (216/1376) assigned to aspirin monotherapy, RR 0.81 (95% CI 0.67-0.97,p=0.024). The composite secondary endpoint of all major ischemic events occurred in 10% of the patients allocated to combined therapy vs. 13% in the aspirin therapy; RR 0.81 (95% CI 0.65-1.01).

Cardiovascular events (MI, stroke)

Gorelick et al.[54] reported that the incidence of recurrent stroke (fatal or non-fatal) with ticlopidine compared to ASA was not significant at 2 years.

ESPS-2[59] was not designed to study the effect of the different treatments on the prevention of MI; when analyzed no statistically significant effect was seen for ASA or extended-release dipyridamole. In ESPS-2,[18] each active treatment arm significantly reduced the incidence of stroke when compared to placebo. The risk reduction with ASA alone vs. placebo was 18.1%; p=0.013. The risk reduction with ERDP alone vs. placebo was 16.3%; p=0.039. When ERDP/ASA was compared to placebo, the risk reduction was 37%; p<0.001. When ASA was the comparator, the relative risk with ERDP/ASA vs. ASA was 23.1%; p<0.006 for the endpoint of stroke. Likewise, a RR of 24.7%; p=0.002 was observed with ERDP/ASA vs. ERDP monotherapy. The combination of ERDP/ASA significantly reduced the RR at 24 months compared to ASA for the outcome of all strokes (9.5% vs. 12.5%; RR 0.76, 95% CI 0.64-0.93; p=0.006) and non fatal strokes (8.3% vs. 11.3%; RR 0.74, 95% CI 0.60-0.91; p=0.004).[57 59] When stroke or TIA were combined, the RR was 24.4% with ASA compared to placebo (p<0.001). Comparing the other arms to placebo, ERDP reduced the rate of stroke or TIA by 20%; (p<0.001) while ERDP/ASA had a RR of 36%; (p<0.001). The combination of ERDP/ASA was superior to ASA alone (RR 18%, p=0.006) and to ERDP alone (RR 20%, p<0.001).[57]

Table 9. Incidence of Primary Outcomes in ESPS-2

Primary Outcome	ERDP (%)	ERDP/ASA (%)	ASA (%)	RR (94% CI)	P value
ERDP vs. ASA					
Stroke	12.8	-	12.5	1.02 (0.85 - 1.22)	NS
Stroke and/or death	19.4	-	20.0	0.97 (0.85 - 1.11)	NS
Death	11.4	-	11.0	1.03 (0.85 - 1.25)	NS
ERDP/ASA vs. ASA					
Stroke		9.5	12.5	0.76 (0.63-0.93)	0.006
Stroke and/or death		17.3	20.0	0.87 (0.75 to 1.00)	NS
Death		11.2	11.9	1.02 (0.84 to 1.23)	NS
ERDP/ASA vs. ERDP					
Stroke	12.8	9.5	-	0.75 (0.61 – 0.91)	0.003
Stroke and/or death	19.4	17.3	-	0.89 (0.77 to 1.03)	NS
Death	11.4	11.2	-	0.99 (0.81 to 1.19)	NS

*Modified from Reference #[34]; ASA=Aspirin, ERDP=Extended Release Dipyridamole; NS=Not Significant.

Table 10. Incidence of Secondary Outcomes in ESPS-2

Secondary Outcome	ERDP (%)	ERDP/ASA (%)	ASA (%)	RR (94% CI)	P value
ERDP vs. ASA					
TIA	13	-	12.5	1.04 (0.87 - 1.24)	NS
Stroke or TIA	23.1	-	22.6	1.02 (0.90 - 1.16)	NS
Myocardial infarction	2.9	-	2.4	1.23 (0.81 - 1.86)	NS
OVE	2.1	-	2.3	0.92 (0.58 - 1.45)	NS
Ischemic events^	16.4	-	16.1	1.02 (0.87 - 1.19)	NS
Vascular death	7.6	-	7.2	1.06 (0.83 -1.35)	NS

Secondary Outcome	ERDP (%)	ERDP/ASA (%)	ASA (%)	RR (94% CI)	P value
Vascular events	19.6	-	19.0	1.03 (0.89 - 1.18)	NS
ERDP/ASA vs. ASA					
TIA	-	10.4	12.5	0.83 (0.69-1.01)	NS
Stroke or TIA	-	18.1	22.6	0.80 (0.70 - 0.92)	0.002
MI	-	2.1	2.4	0.90 (0.57 - 1.41)	NS
OVE	-	1.3	2.3	0.55 (0.33 - 0.94)	0.025
Ischemic events^	-	12.5	16.1	0.77 (0.65 - 0.92)	0.003
Vascular death	-	7.1	7.2	0.99 (0.77 - 1.27)	NS
Vascular events	-	14.9	19.0	0.78 (0.67 - 0.91)	0.001
ERDP/ASA vs. ERDP					
TIA	13.0	10.4	-	0.80 (0.66-0.97)	0.021
Stroke or TIA	23.1	18.1	-	0.78 (0.69-0.90)	<0.001
MI	2.9	2.1	-	0.73 (0.48 - 1.12)	NS
OVE	2.1	1.3	-	0.60 (0.35 - 1.03)	NS
Ischemic events^	16.4	12.5	-	0,76 (0.64 - 0.90)	0.002
Vascular death	7.6	7.1	-	0.94 (0.74 - 1.20)	NS
Vascular events	19.6	14.9	-	0.76 (0.65 - 0.89)	<0.001

*Modified from Reference #[34]; ERDP=Extended release dipyridamole; ^Fatal and non-fatal stroke, MI or sudden death; OVE=other vascular events; TIA=transient ischemic attack; NS = Not Significant.

Outcome events defined post hoc in the ESPRIT[21] trial were fatal and non-fatal ischemic stroke and all cardiac events (fatal and non-fatal MI, sudden death, and death from cardiac causes). While more patients experienced first ischemic stroke in the ASA alone group vs. ERDP/ASA group, the difference was not significant. The same is true with the incidence of first cardiac event. A higher incidence for first cardiac event was seen in the ASA group, although again the difference was not significant.

The MATCH[19] trial found that the incidence of ischemic stroke (fatal or non-fatal) during the 18-month study period was the same with clopidogrel plus aspirin compared to clopidogrel alone. Overall, the combination of ASA and clopidogrel did not significantly lower the incidence of ischemic strokes, MI, or vascular death (12% vs. 12%; RR 0.94, CI 0.83-1.06). Two percent of patients in both groups experienced a fatal or non fatal MI. (See Table 11 for other outcomes.)

Table 11. MATCH[19] Trial: Number of patients (%) With Events

Primary endpoints†	clopidogrel + ASA n= 3797 n (%)	clopidogrel n=3802 n (%)	RR (95% CI) p value
Ischemic stroke, MI, vascular death,* rehospitalization for an acute ischemic event**	596 (16)	636 (17)	0.94 (0.85-1.04) NS
MI (fatal or not)	59 (1.6)	62 (1.6)	0.95 (0.67-1.36) NS
Ischemic stroke (fatal or non-fatal)	299 (7.9)	319 (8.4)	0.94 (0.81-1.09) NS
Other vascular death*	69 (1.8)	74 (1.9)	0.93 (0.67-1.29) NS
Rehospitalization for acute ischemic event**	169 (4.5)	181 (4.8)	0.93 (0.76 1.15) NS

MI=myocardial infarction; * Includes hemorrhagic death of any origin; ** includes unstable angina pectoris, worsening of peripheral arterial disease requiring therapeutic intervention or urgent revascularization, or TIA; † For every component of the primary endpoint, only the event regarded as first outcome from the composite was counted, NS = Not Significant; RR=Relative Risk.

The TASS trial[20] demonstrated a 5-year event rate for nonfatal stroke of 10.2% (156/1529) for ticlopidine and 12.3% (189/1540) for aspirin (RR 0.83, 95% CI 0.68-1.02). The 5-year event rate for fatal stroke was 1.0% (16/1529) for ticlopidine vs. 1.5% (23/1540) for aspirin (RR 0.70, 95% CI 0.37-1.32). Combining the two endpoints, the incidence was 11.2% for ticlopidine and 13.8% for aspirin (RR 0.84, 95% CI 0.69-1.01; p=0.063). Reduction in the stroke incidence was seen in both women and men. (Refer to Key Question 3, Gender section, below.)

Invasive vascular procedure failure (including need for additional invasive vascular procedures)

Gorelick et al.[54] did not evaluate the endpoint of invasive vascular procedures or failures.

The endpoint of vascular procedures alone was not evaluated in ESPS-2.[57] However, the endpoint of "other vascular events" (OVE) including deep venous thrombosis, pulmonary embolism, peripheral arterial occlusion, and venous retinal vascular events occurred 148 times in the study, of which 48 (32%) were peripheral arterial occlusion. Aspirin and or extended-release dipyridamole reduced the incidence of OVE compared to placebo and that effect was even greater with the combination of ERDP/ASA (RR with ASA alone, 31.6%, (p=0.10); ERDP alone, 36.7%, (p=0.053); ERDP/ASA, 61.7%, (p <0.001).

In MATCH,[19] using the intention-to-treat analysis, the composite primary endpoint including rehospitalization for acute ischemic events (such as unstable angina pectoris, worsening of PAD requiring therapeutic intervention, urgent revascularization, or TIA) was similar for clopidogrel plus aspirin compared to clopidogrel alone (15.7% vs. 16.7%; RR 9.4, 95% CI 0.85-1.04). When rehospitalization for acute ischemic event was evaluated as a secondary endpoint using a log-rank test, no difference was seen between the two groups (4% (169/3797) vs. 5% (181/3802); RR 0.93, 95% CI 0.76-1.15).

The incidence of invasive vascular procedures or failures as a prespecified endpoint was not studied in TASS.[20]

Systematic Reviews:

The systematic review done by Tran et al.[35] reviewed antiplatelet treatment in patients with CVA, ACS or PAD. No analysis was performed and only subjective interpretation of the evidence was provided.

Hankey and colleagues reported in a Cochrane Review[26] and two journal articles[25 36] on four trials with a total of 22,656 high risk vascular patients that the odds ratio of any stroke was significant for the thienopyridines compared to aspirin (5.7% vs. 6.4%; OR 0.88, 95% CI 0.79-0.98; p=0.02, NNT=138). Furthermore, the reduction for ischemic stroke was of similar magnitude but did not reach conventional levels of statistical significance (OR 0.90, 95% CI 0.81-1.01).

One systematic review[36] comparing the thienopyridines against aspirin in high-risk patients included four trials with 22,656 patients. Follow-up was for 12 to 40 months. Aspirin was compared with ticlopidine in three of the trials (n=3471 patients). Pooled results indicated that ticlopidine or clopidogrel produced a modest decrease in the odds of serious vascular events compared to aspirin (12% vs. 13%;OR 0.91, 95% CI 0.84 -0.98; p=.01). No significant trends in favor of clopidogrel or ticlopidine compared to aspirin were seen for ischemic stroke, MI, vascular or unknown cause of death, or death from any cause. The risk of stroke (any type) was decreased in the thienopyridine group compared to aspirin (10.4% vs. 12.0%; OR 0.86, 95% CI 0.75-0.9). The thienopyridines and aspirin produced a similar benefit for the composite endpoint (all vascular events) in patients presenting specifically with stroke or TIA (16.8% for thienopyridines vs. 18.3% for aspirin; OR 0.90, 95% CI 0.81-1.00).

One collaborative meta-analysis[2] reviewed the effects of antiplatelet therapy (primarily ASA) among high risk patients. Trials representing the medications of interest for this paper were minimal and no conclusions could be drawn from that analysis.

Another meta-analysis[55] combined dipyridamole plus ASA trials (14 trials with 5317 patients) from the 1994 Antiplatelet Trialists' Collaboration[47] (ATC) with the ESPS-2 trial. Although the formulation of dipyridamole plus ASA differed between the two trials, when vascular events and nonvascular deaths were collectively assessed, there was a further reduction in the odds of nonfatal stroke, from 12% to 23%, with the dipyridamole plus ASA compared to aspirin alone. A nearly significant 10% reduction in the odds of all vascular events was also seen, although the reduction was primarily due to fewer nonfatal strokes. When the ESPS-2 results were combined with the CV trials, a reduction in vascular event rates was reported, primarily due to 25% fewer non-fatal strokes.

The investigators of ESPRIT[21] conducted a meta-analysis in patients with cerebral ischemia of presumed arterial origin for the composite outcome of vascular death, non-fatal stroke, or non-fatal myocardial infarction. The total number of trials was 6 (4 of which were done pre-ESPS-2[18]). The overall risk ratio for that endpoint was 0.82 (95% CI 0.74-0.91). The respective RR for that same endpoint for ESPS-2[18] was 0.78 (95% CI 0.67-0.91) compared to RR 0.78 (95% CI 0.64-0.96) for the ESPRIT[21] trial. The authors suggested that the results from the ESPRIT trial are consistent with that of ESPS-2 in terms of the added benefit seen with ERDP plus aspirin compared to aspirin alone.

Key Question 1c. Outcomes: Symptomatic Peripheral Vascular Disease

In patients with symptomatic peripheral vascular disease what is the comparative efficacy of the newer antiplatelet agents in mortality (all-cause and

cardiovascular), cardiovascular events (MI, stroke), invasive vascular procedure failure (including the need for additional invasive vascular procedures)?

Overall Summary of Evidence for comparative effectiveness and safety of the newer antiplatelet agents in patients with peripheral vascular disease (PVD)

Efficacy Trials:

- No head-to-head trials are available; therefore no comparative conclusions can be made between these newer antiplatelet agents in the setting of PVD.
- Active-controlled trial: One high-quality, multicenter randomized controlled trial[22] (RCT) was included.

The CAPRIE[22] study compared clopidogrel 75 mg to ASA 325 mg daily for reducing the risk of future thrombotic events (MI, stroke, or vascular death). Three subsets of patients were enrolled e.g., those with a history of recent MI, recent ischemic stroke, or symptomatic PAD. Treatment with clopidogrel did not significantly reduce the risk of vascular death or death from any cause compared with treatment with aspirin. The study did find a small absolute benefit of clopidogrel over aspirin (ARR = .51%, NNT = 196) in reducing the combined risk of ischemic stroke, MI, and vascular death in high-risk patients when treated for up to 3 years (mean 1.91 years) compared to aspirin in patients with atherosclerotic vascular disease. When the incidence of the primary outcome was analyzed by clinical subgroup (according to qualifying event), there was a suggested benefit of clopidogrel vs. aspirin in patients with PAD (3.71% vs. 4.86%; RRR 23.8%, p=0.0028) but a similar benefit was not found in the stroke or MI subgroups. While a statistical analysis suggested heterogeneity (i.e., an apparent difference in benefit across the three vascular conditions), the reason for the heterogeneity-- and the extent to which that might exist -- remains unclear. The findings from these analyses should be interpreted with caution as the trial was not powered to detect difference between the three clinical subgroups and there was also considerable overlap in the atherothrombotic history of the patients included in the trial. The percentage of patients that permanently discontinued the study drug early was 21.2% for reasons other than the occurrence of an outcome event.

Clopidogrel was favored over aspirin but the upper CI of one raises the possibility that clopidogrel is not more beneficial than aspirin in terms of the composite primary outcome.

Primary Outcome—clopidogrel vs. ASA (36 months)

- Ischemic stroke, MI or vascular death: 9.8 vs. 10.7; RR 0.92, 95% CI 0.84-1.00

Clopidogrel was favored over aspirin for the secondary outcomes but none were statistically significant.

Secondary Outcomes— clopidogrel vs. ASA (36 months)

- Ischemic stroke, MI, amputation or vascular death: 10.2% vs. 11.0%; RR 0.93, 95% CI 0.86-1.01
- Vascular death: 3.7% vs. 4.0%; RR 0.93, 95% CI 0.80-1.07

- Any stroke, MI or death from any cause: 11.9% vs. 12.6%; RR 0.94, 95% CI 0.87-1.01
- Death from any cause: 5.9% vs. 6.0%; RR 0.98, 95% CI 0.88-1.10

Safety/Adverse Events:

In the CAPRIE[34 60] trial, the incidence of rash and diarrhea was significantly higher in the clopidogrel group than the aspirin group. Patients taking aspirin had a higher incidence of indigestion/nausea/vomiting than patients in the clopidogrel group. The number of patients reporting hematological adverse events was rare in both the clopidogrel and aspirin groups. No cases of thrombotic thrombocytopenic purpura (TTP) were reported in either group. There was no difference in the number of patients reporting any bleeding disorder in the clopidogrel group compared with the aspirin group. More patients in the aspirin treatment group than in the clopidogrel treatment group experienced GI hemorrhage.

In the CAPRIE[60] 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 GI event: 3.21% for clopidogrel and 4.02% for aspirin. Early permanent discontinuation rates for skin and appendage disorders (primarily rash) were more frequent with clopidogrel than with aspirin (1.52% vs. 0.76%).

clopidogrel vs. aspirin

- Any bleeding disorder: 9.3% vs. 9.3%; RR 1.00, 95% CI 0.91-1.09
- Rash: 6.0% v. 4.6%; RR 1.31, 95% CI 1.16-1.47
- Diarrhea: 4.5% vs. 3.4%; RR 1.33, 95% CI 1.15-1.53
- Indigestion/nausea/vomiting: 15.0% vs. 17.6%; RR0.85, 95% CI 0.80-0.91

Subgroups:

No conclusion about the comparative effectiveness or safety of the newer antiplatelet agents based on age, gender, race, comorbidities or other medications can be made from this body of evidence in patients with PVD.

- **Head-to-Head Trials:** No relevant head-to-head trials were identified.

- **Active-controlled trials: (poor/fair quality)**

One matched-controlled trial[61] (judged to be of poor quality primarily due to the variation in the frequency and duration of antiplatelet agents) was identified that compared aspirin to ticlopidine in patients with PVD.

- **Active-controlled trials**: (good quality)

The Clopidogrel vs. ASA in Patients at Risk for Ischemic Events (CAPRIE)[22] trial compared clopidogrel 75 mg to aspirin for reducing subsequent thrombotic events (MI, stroke, or vascular death) in 19,185 high-risk patients with documented atherosclerotic vascular disease. In

this randomized double-blind study, eligible patients had a history of recent ischemic stroke (n=6431), MI (n=6302) or established PAD (n=6452) and were followed for 1 to 3 years (mean 1.91 years). (Details of the CAPRIE trial are included in Evidence Table A1 and Quality Table A2.)

Mortality (All-cause and cardiovascular)

In CAPRIE,[22] the incidence of death from any cause was similar at 36 months between clopidogrel vs. ASA (5.9% vs. 6.0%), as was the incidence of vascular death (4.0% vs. 3.7%).

Combined Outcomes (fatal and non-fatal)

In CAPRIE,[22] the combined endpoint of ischemic stroke, MI, and vascular death, an intention-to-treat analysis resulted in an ARR of .51%; RR.92 (95% CI 0.84-1.00, p=0.0430) at 36 months in favor of clopidogrel. (Additional outcomes from the CAPRIE trial are depicted in Table 12.)

Table 12. CAPRIE* Trial: Comparison of Outcome Event Cluster Rates

Outcome event cluster	Clopidogrel Event rate per year,%	ASA Event rate per year, %	Relative Risk (95% CI) P value
Primary Outcome			
Ischemic stroke, MI or vascular death	5.32	5.83	0.92 (0.84-1.00) 0.043
Secondary Outcomes			
Ischemic stroke, MI, amputation, or vascular death	5.56	6.01	0.93 (0.86-1.01) NS
Vascular death	1.90	2.06	0.93 (0.80-1.07) NS
Any stroke†, MI, or death from any cause	6.43	6.90	0.94 (0.87-1.01) NS
Death from any cause	3.05	3.11	0.98 (0.88 -1.10) NS

*Modified from Reference #22; † Includes primary intracranial hemorrhage; NS = Not Significant.

Cardiovascular events (MI, stroke)

Stroke as an independent endpoint was not included in CAPRIE.[22] (Refer to Table 12 for the primary outcome event cluster rate of ischemic stroke, MI, or vascular death and the secondary outcome event clusters.) (Patients with a history of a stroke as the qualifying event in CAPRIE are discussed under Key Question 3, Comorbidities.)

The Health Technology Assessment report[34] published in October 2004 extracted data from the ATT meta-analysis[12] that was related to the CAPRIE trial. Due to the limits of the

confidence intervals, a reliable estimate of the true size of any difference between clopidogrel and aspirin could not be determined in the individual outcomes that were evaluated which included serious vascular event, death from any cause, non-fatal MI, non-fatal stroke, vascular death, non-vascular death, non-fatal major bleeds, non-fatal major bleeds and all major bleeds.

In CAPRIE, a subgroup analysis[62] showed that acute myocardial infarction occurred in 5.04% of the ASA group compared to 4.2% of the clopidogrel group (RRR 19.2%; p=0.008). The relative benefit of clopidogrel was constant over time (follow-up of 1 to 3 years) and was seen across all patient subgroups. (Refer to Key Question 3, Comorbidities.)

Some preliminary results derived from poster presentations[63-66] provide additional, analyses from the CAPRIE trial. However, we note the results have not yet been subject to peer review process as they have yet to appear in a peer-reviewed journal. These results include a reported benefit of clopidogrel in lacunar (RRR 9.9%, 95% CI -14.4-29.1) and non-lacunar strokes (RRR 3.0%, 95% CI -12.8-16.5), although the RRR was less in patients with recent MI than in patients presenting with prior stroke or with PAD and not statistically significant. One analysis suggests that the 8.7% RRR with clopidogrel compared to aspirin seen for the primary endpoint in the CAPRIE study is consistent among all patients with atherosclerotic vascular disease and not less in patients with recent MI. A multivariate model controlling for baseline features suggested that patients on lipid-lowering therapy for elevated cholesterol (n=1080) had a 20% RRR in vascular death, MI, stroke, and rehospitalization for ischemia or bleeding compared to those not on lipid lowering therapy (p=0.026). A favorable RRR was also seen in TIA, unstable TIA, and hospitalization.

Invasive vascular procedure failure (including need for additional invasive vascular procedures)

In CAPRIE,[22] amputation occurred in 99 patients (clopidogrel, n=55; placebo, n=47). Amputation was one of the outcome events included in the cluster endpoint along with ischemic stroke, MI, or vascular death. The incidence of this cluster endpoint at 36 months was not significant (RRR 7.6%, 95% CI-0.8 -15.3; p=0.076).

Systematic Review:

One systematic review[35] evaluated various regimens of antiplatelet treatment in patients with PAD, ACS, or CVA. No analysis was performed in the study but rather recommendations for practice were offered. The authors concluded that aggressive antiplatelet therapy is needed for patients with PVD and that the first-line oral antiplatelet therapy should be aspirin or clopidogrel, with clopidogrel recommended for patients who cannot take or tolerate aspirin. Because a high proportion of patients with PAD have coexisting CAD, ERDP/ASA was not recommended unless patients had a history of stroke or TIA.

Robless et al.[67] evaluated 24 randomized controlled trials in a systematic review comparing antiplatelet treatment with placebo for the prevention of MI, stroke, or vascular death in patients with PVD. Of the 24 trials, five trials compared different antiplatelet regimens with ASA in patients with PVD. Of those five trials, only one trial (CAPRIE) met the inclusion criteria for this drug class review. The four trials excluded from this review either had outcomes that were not of interest, included a different formulation than ERDP/ASA, or were based on

unavailable reports. In any case, Robless et al.[67] reported that the incidence of vascular events was 8.4% with ASA (292/3467) compared to 6.6% with the second antiplatelet regimen (ticlopidine, clopidogrel, or dipyridamole plus ASA). The pooled Peto odds ratio for vascular events was 0.76 (95% CI 0.64-0.91, p=0.003) favoring the second antiplatelet regimen. The most notable results were from the CAPRIE study, in which 215 (6.7%) of 3223 patients in the clopidogrel group suffered a vascular event compared with 277 (8.6%) of 3229 patients in the aspirin group. For the CAPRIE subgroup, the odds ratio for vascular events was 0.77 (95% CI 0.64-0.92) favoring clopidogrel (p=0.0028). (Refer to Key Question 3, Comorbidities for more details.)

Key Question 2. Safety or Adverse Events

For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or TIA, or symptomatic peripheral vascular disease do antiplatelets differ in safety or adverse events?

The assessment of whether the newer antiplatelet agents differ in safety or adverse events included three meta-analyses[25 26 36] and multiple large, randomized controlled trials including CURE,[12] PCI-CURE,[15] CREDO,[16] ARMYDA-2,[17] CHARISMA,[13] CLASSICS,[14] MATCH,[19] TASS,[20] ESPS-2,[57] ESPRIT,[21] and CAPRIE.[22] All the antiplatelet trials had a high percentage of adverse events including those with aspirin. Aspirin was most often noted to cause GI- related symptoms such as dyspepsia, nausea, and vomiting. The extent of use with the newer antiplatelet agents in the major clinical trials includes the following: extended release dipyridamole/ASA (ERSP/ASA) was evaluated in 6,602 patients for a 2-year duration in the ESPS-2[57] trial and 3.5 years in the ESPRIT trial.[21] Clopidogrel was evaluated in more than 23,400 patients including over 24,600 treated for 1 year or more (CAPRIE,[22] CURE,[12] and CHARISMA[33] trials). Ticlopidine was evaluated in more than 4000 patients for 5 years in the TASS[20] and the Canadian American Ticlopidine Study (CATS)[68] trials. The CATS[68] trial did not meet the inclusion criteria for this drug class review, but the incidence of ticlopidine-induced neutropenia from that trial was included in this report. (Refer to the neutropenia section below.)

Overall adverse effect reported

Aspirin increases the risk of dyspepsia and GI hemorrhage. A primary concern with the newer antiplatelet agents is the incidence and severity of bleeding. In the CURE[12] trial, GI events (abdominal pain, dyspepsia, gastritis, and constipation) were higher with ASA than clopidogrel plus aspirin (12.5% vs. 11.7%). In the CAPRIE[60] trial, the overall incidence of GI events (e.g. abdominal pain, dyspepsia, gastritis, and constipation) was 27.1% with clopidogrel and 29.8% with aspirin (p= <0.001). In the same trial, ASA was associated with GI hemorrhage in 2.7% of patients and with GI hemorrhage requiring hospitalization in 1.1%; with clopidogrel, those rates were 2.0% and 0.7%, respectively. Intracranial hemorrhage occurred in 0.4% of patients treated with clopidogrel and 0.5% with ASA.

Hankey and colleagues reported in a Cochrane Review[26] and two journal articles[25 36] on four trials of thienopyridines and ASA use in 22,656 patients at high risk for vascular disease.

Two trials[20 22] included in the meta-analysis were evaluated for this drug review. In the meta-analysis, ASA had a higher incidence of GI-related symptoms including indigestion, nausea and vomiting. The incidence of diarrhea, rash, and neutropenia was greater with the thienopyridines. (Refer to Table 13.)

Table 13. Meta-analysis:[25 26 36] Comparing adverse events: Thienopyridines vs. Aspirin in High-Risk Patients

Adverse events	Incidence of adverse events (%)		
	Thienopyridine	ASA	OR, 95% CI
Intracranial hemorrhage (hemorrhagic stroke)	0.3	0.4	0.82, 0.53 – 1.27
Extracranial hemorrhage (including GI hemorrhage)	8.84	8.86	1.0, 0.91 - 1.09
Severe extracranial hemorrhage	1.02	1.06	0.96, 0.73 – 1.27
Gastrointestinal hemorrhage	1.8	2.5	0.71, 0.59 – 0.86
Neutropenia*			
Clopidogrel	0.1¶ †	0.2¶†	0.63, 0.29 -1.36¶†
Ticlopidine	2.3¶†	0.8¶†	2.7, 1.5 - 4.8
Severe neutropenia**			
Clopidogrel	0.05	0.04	1.25, 0.34 – 4.61
Ticlopidine	0.9	0	7.5, 2.5 – 22.3
§Thrombocytopenia			
Clopidogrel	0.26	0.26	1.00 0.57-1.74¶
Severe thrombocytopenia†	0.19	0.10	1.77,0.84 – 3.71
Diarrhea			
Clopidogrel	4.5	3.4	1.3, 1.2 - 1.6
Ticlopidine	20.4	9.9	2.3, 1.9 - 2.8
Skin rash			
Clopidogrel	6.0	4.6	1.3, 1.2 - 1.5
Ticlopidine	11.8	5.5	2.2, 1.7 - 2.9
Indigestion, nausea, vomiting	14.8	17.1	0.84, 0.78 – 0.90

* <1.2 x 10^9/L; ** <0.45 x 10^9/l; § <100 x 10^9/L; † <80x 10^9/L; ¶ provided by Hankey et al.[25]; †provided by Hankey et al.[36]

Although the thienopyridines have relatively similar adverse effect profiles, there are notable differences. Ticlopidine may cause neutropenia while this has not been noted to the same degree as with clopidogrel. (See discussion on neutropenia Specific Adverse Events or Withdrawal due to Specific Adverse Events section) Diarrhea and rash are more common with the thienopyridines, particularly with ticlopidine, than with aspirin.

In the CURE[12] trial, the incidence of any adverse events related to skin and appendage disorders was higher with clopidogrel plus ASA compared to placebo plus ASA (4.0% vs. 3.5%; $p \leq 0.05$).[34] In the Cochrane meta-analysis,[26] clopidogrel was associated with 30% more rash and diarrhea compared to aspirin, whereas ticlopidine increased the rate of rash and diarrhea by more than twofold over aspirin. In CAPRIE,[22] the incidence of skin and appendage disorders with clopidogrel was 15.8% (0.7% serious) and the corresponding rate with ASA patients was 13.1% (0.5% serious) ($p < 0.01$).[10]

In the ESPS-2[57] trial, the adverse event rate was high for all medications, including the placebo. Overall, adverse effects (one or more) occurred in 79.7%, 78.9%, 80.2% and 70.1% patients on ERDP/ASA, ERDP, ASA and placebo, respectively. Headache, dizziness, and GI symptoms were the most frequent adverse events reported for ERDP/ASA. (Refer to Table 14.) Headache occurred more often in patients taking ERDP alone or ERDP in combination with aspirin than the aspirin alone group. The frequency of diarrhea was significantly higher in

patients treated with ERDP alone or ERDP with aspirin compared to aspirin alone or to placebo ($p<0.001$). Nausea and vomiting were also significantly higher in the ERDP/ASA group than the aspirin alone group. The incidence of bleeding events (any site) was nearly twice as high in both aspirin groups compared to ERDP or placebo. The incidence of adverse events reported in 2x2 factorial design are depicted in Table 15.

In the TASS[22] trial, diarrhea occurred in 20% of the patients taking ticlopidine and 10% of those taking aspirin. Rash developed in 12% of the patients taking ticlopidine and 5% of those taking aspirin. Severe but reversible neutropenia occurred in 13 patients assigned to ticlopidine and in none in the aspirin group. Mild-to-moderate neutropenia occurred in 22 patients in the ticlopidine group and 12 patients in the aspirin group.

Table 14. ESPS-2:[18,57] Percentage of Patients With Most Common Adverse Events

Adverse events	ERDP/ASA N=1650	ERDP N=1654	ASA N=1649	Placebo N=1649
Headache	38.2	37.2	33.1	32.4
Dyspepsia	17.6	16.6	17.2	16.1
Gastric pain	16.6	14.5	14.7	13.3
Nausea	15.4	14.8	12.4	13.7
Vomiting	8.1	7.2	5.6	6.6
Diarrhea	12.1	15.4	6.6	9.3
Dizziness	29.5	30.1	29.2	30.9
Bleeding any site (total)	8.7	4.7	8.2	4.5

ERDP= Extended-release dipyridamole, ASA= aspirin.

Table 15. * Incidence of Other Adverse Events in ESPS-2

Adverse Event	ERDP (%)	ERDP/ASA (%)	ASA (%)	RR (94% CI)	P value
ERDP vs. ASA					
Any adverse event	62.5	-	60.0	1.04 (0.99 – 1.10)	0.144
Gastrointestinal event	30.5	-	30.4	1.00 (0.90 – 1.11)	0.956
Headache	37.2	-	33.1	1.12 (1.02 – 1.23)	0.014
Dizziness	30.1	-	29.2	1.03 (0.93 – 1.15)	0.554
ERDP/ASA vs. ASA					
Any adverse event	-	64.0	60.0	1.07 (1.01 – 1.12)	0.019
Gastrointestinal event	-	32.8	30.4	1.08 (0.97 – 1.19)	0.148
Headache	-	29.5	29.2	1.15 (1.05 – 1.26)	0.002
Dizziness	-	38.2	33.1	1.01 (0.91 – 1.12)	0.857
ERDP/ASA vs. ERDP					
Any adverse event	62.5	64.0	-	1.02 (0.97 – 1.08)	0.376
Gastrointestinal event	30.5	32.8	-	1.07 (0.97 – 1.19)	0.163
Headache	37.2	38.2	-	1.03 (0.94 – 1.12)	0.553
Dizziness	30.1	29.5	-	0.98 (0.88 – 1.09)	0.681

*Modified from Reference #52; ERDP=extended release dipyridamole; ASA=aspirin; RR=Relative Risk; CI=Confidence Interval.

Withdrawals due to adverse events

In the head-to-head PCI trials that compared clopidogrel to ticlopidine, rash was the most frequent reason for discontinuing these medications, more so with ticlopidine than clopidogrel.[14 43] In Taniuchi et al.[43] failure to complete 2 weeks of concurrent therapy was greater with ticlopidine and aspirin than with clopidogrel and aspirin (ticlopidine, 3.64% vs. clopidogrel, 1.62%; p=0.043).

In the 28 day CLASSICS[14] 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% vs. 9.1%; p =0.005). Gastrointestinal disorder was the most frequent non-cardiac reason for discontinuing therapy, with incidences of 2.6% in ticlopidine users and and 2.4% in clopidogrel no loading dose users. The incidence of skin disorders, primarily rash, in 2.6%, 0.9%, 0.6% the ticlopidine group, clopidogrel no-loading dose group and clopidogrel loading-dose group, respectively. 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; three of them had received heparin concomitantly.

In the CURE[12] trial, 21.1% of the patients in the clopidogrel plus aspirin group discontinued the study medication permanently, compared to 18.8% in the placebo plus aspirin group (p=0.001). The discontinuation rates due to adverse events were comparable between clopidogrel and placebo. Minor bleeding (defined as other hemorrhages requiring interruption of the drug regimen) was significant with clopidogrel compared to placebo (5.1% vs. 2.4%; p<0.001, respectively).

In the CREDO[16] study, the reasons patients (n=94) stopped the study medications prior to day 28 were not provided. Following PCI procedure, approximately 46% of the patients in both groups permanently discontinued treatment. The incidence of an adverse event was the reason for permanently discontinuing the study medication in 34.5% clopidogrel users and 28.3% in those receiving placebo (p=0.002).

In ARMYDA[17] trial, no significant side effects occurred in either the high or the conventional loading dose clopidogrel group that would warrant interruption of clopidogrel. No postprocedural thrombocytopenia with a platelet count $<70 \times 10^9$/L was observed.

In CHARISMA[13] 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 ESPS-2[57] trial, treatment discontinuation was primarily due to adverse events. Patients who stopped ERDP/ASA or ERDP due to headache most often did so during the first month of therapy. At 30 days, GI adverse events accounted for 56.2% of treatment cessation in the two ERDP groups (123/219) and 38% (46/121) in the non-ERDP groups.

In ESPRIT[21] trial, a large number of patients (34%) discontinued the combination of aspirin and dipyridamole due to side-effects, primarily due to headaches (26%). Of the patients taking aspirin alone, 184 (13%) discontinued therapy, primarily due to a medical reason, such as a new transient ischemic attack, stroke or an indication for oral anticoagulant therapy. Several different treatment regimens have been utilized to attempt to decrease the incidence of headache associated with dipyridamole including concurrent treatment with analgesics as well as initiating

a titration regimen starting with a lower daily dose of dipyridamole. One trial that evaluated the success of a titration schedule was conducted by Lindgren et al.[69] The trial was randomized, open-label design. The authors evaluated whether initiating a titration treatment with 75 mg ASA in the AM and the combined ASA 25 mg and modified release dipyridamole in the evening would reduce the prevalence of headache compared to the standard treatment of combined ASA 25 mg plus modified release dipyridamole 200 mg twice a day. The study duration was 20 days and enrolled 60 individuals with ischemic stroke or TIA within the previous 3 months. The primary endpoint of the study was the proportion of patients reporting moderate to severe headache during days 7-19. Although the incidence of the primary endpoint did not differ between the standard and titration groups, this study was underpowered for definitive conclusions regarding any possible differences between the treatment groups for primary and secondary endpoints. Studies involving larger number of patients would need to be conducted to determine whether dose titration in the initial phase of modified release dipyridamole treatment would be of benefit in lowering the prevalence of dipyridamole induced headache and thus, resulting in improved adherence to the medication.

In the CAPRIE[60] 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 GI event: 3.21% for clopidogrel and 4.02% for aspirin. Early permanent discontinuations rates for skin and appendage disorders (primarily rash) were more frequent with clopidogrel than with aspirin (1.52% vs. 0.76%).

In the TASS[20] study, discontinuation due to adverse effects (primarily diarrhea and rash) occurred in 14.5% of patients on ticlopidine and 6.1% in those taking ASA ($p<0.5$). Patients more often prematurely terminated ticlopidine than aspirin (51.6% vs. 47%; $p<0.05$).

In summary, headache and diarrhea occurred more frequently and resulted in higher withdrawals rates with ERDP/ASA and ERDP compared to placebo or ASA alone. Rash and diarrhea were the most common reasons to stop ticlopidine, more so than that with clopidogrel. Overall, clopidogrel was better tolerated than ticlopidine.

Serious adverse events reported

Intracranial hemorrhage (ICH) is an uncommon but often fatal or severely debilitating complication of chronic antithrombotic therapy. In the MATCH[19] trial, the combination of clopidogrel with aspirin increased the rate of central nervous system bleeding by 61%, $p=0.06$ compared to clopidogrel alone.[70] In the CURE[12] trial, a similar trend was observed although too few ICHs occurred to meaningfully assess.[70] Table 16 depicts the rates of ICH reported in the larger clinical trials included in this paper.

Table 16.*CNS Bleeding Rates During Antiplatelet Therapy: Aspirin and Thienopyridines

Trial	Population	Mean Age (y)	ASA	Clopidogrel / Ticlopidine	ASA + Clopidogrel	Rate Ratio
CAPRIE[22]	Vascular disease	63	0.3%/y (n=47)	0.2%/y (n=24)	N/A	…
CURE[12]	ACS	64	0.1%/y (n=5)	N/A	0.15%/y (n=7)	1.4
AAASPS[54]	Recent ischemic stroke	61	0.2%/y (n=3)	0.3%/y (n=4)	N/A	…
MATCH[19]	Recent ischemic stroke or TIA	66	N/A	0.4%/y (n=25)	0.7%/y (n=40)	1.6
CHARISMA[13]	Clinically evident CV disease or multiple risk factors	64	0.15%/y (n=27)	N/A	0.15%/y (n=26)	---
TASS**[20]	Recent ischemic stroke or TIA	63	0.15%/y (n=7)	0.15%/y (n=7)	N/A	---

*Adapted from Hart et al.[71]; Rates are based on published results using total patient exposure reported for primary outcome and therefore, actual rates may be slightly lower. TIA = transient ischemic attack; ACS =acute coronary syndrome; CV = cardiovascular; N/A = Not applicable; ** follow-up period was not clearly defined, 3 years was used in calculation, the number of patients exposed to ticlopidine was 1518 and to ASA was 1527.
ASA dosages: CAPRIE=325 mg/d; CURE=75-325 mg/d; AAASPS=650 mg/d; MATCH=75 mg/d; CHARISMA =75-162 mg; TASS= 65- mg twice a day, ARMYDA-2 intracranial bleeding was included in the major bleeding—no postprocedural major bleeding occurred.
CNS bleeds were not reported in the CREDO trial; In ESPS II, the rate of CNS bleeding was reported as 0.4%/y with aspirin 25 mg twice daily and as 0.3%/y with aspirin 25 mg plus extended-release dipyridamole 200 mg twice a daily; however, these absolute rates are underestimates because neuroimaging was not performed in 27% of stroke events.
All study participants were African-Americans; number of CNS bleeds has not been published, rates estimated based on mean follow-up of 1.54 years. Authors of the original study (Hart et al.[71]) stated this data was obtained via personal communication with Gorelick and Richardson from Reference #53.

In the CURE[12] trial, major bleeding was statistically more frequent with clopidogrel and aspirin than with placebo and aspirin alone (3.7% vs. 2.7%; RR=1.4, 95% CI 1.1-1.7, p=0.001). The most common types of bleeding were GI-related (1.3% with clopidogrel vs. 0.7% with ASA) and bleeding at arterial puncture sites. Major bleeding with clopidogrel plus aspirin occurred early in the study. Within 30 days of randomization, the rate of major bleeding with clopidogrel plus aspirin was 2.0% and 1.5% with placebo plus aspirin (RR 1.31, 95% CI 1.01-1.70). Major bleeding was also seen 30 days after randomization for clopidogrel and aspirin but, as with the earlier bleeding rates, did not reach statistically significance (1.7% vs. 1.1%) (RR 1.48, 95% CI 1.10-1.99). The incidence of all types of bleeding decreased over the duration of the study. (Refer to Table 17.)

In the CURE[12] trial, life-threatening bleeding occurred with clopidogrel plus ASA more often than with placebo plus ASA, but the result was not statistically significant (2.2% vs. 1.8%;

p=0.13, RR=1.21, 95% CI 0.95-1.56). There was no difference in the number of fatal bleeding episodes, bleeding requiring surgical intervention, or hemorrhagic strokes between the two groups. The number of patients requiring 2 or more blood transfusions was greater for clopidogrel plus aspirin (n=177, 2.8%) than placebo and aspirin alone (n=137, 2.2%, p=0.02). The investigators reported that for every 1000 patients treated with clopidogrel plus aspirin for a mean of 9 months, 6 would require a blood transfusion.

Table 17. CURE[72]: Incidence of All Types of Bleeding Per Months of Therapy

Months of therapy	Risk of bleeding (life-threatening, major, minor, other) N/total number of subjects (%)	
	Clopidogrel	Placebo
0-1	599/6259 (9.6)	413/6303 (6.6)
1-3	276/6123 (4.5)	144/6168 (2.3)
3-6	228/6037 (3.8)	99/6048 (1.6)
6-9	162/5005 (3.2)	74/4972 (1.5)
9-12	73/3841 (1.9)	40/3844 (1.0)

Even though the CURE[12] trial was not powered to detect differences in bleeding rates by aspirin dose, a post hoc observational analysis[23] evaluated the dose-response bleeding risk of the various aspirin doses when given concurrently with clopidogrel. Major bleeding was significantly higher with increasing aspirin doses both in the placebo group (ASA ≤ 100 mg, 1.9%; ASA 101-199 mg, 2.8%; ASA ≥ 200 mg, 3.7%; p=0.0001) and the clopidogrel group (ASA ≤ 100 mg, 3.0%; ASA 101-199 mg, 3.4%; ASA ≥ 200 mg, 4.9%; p=0.0009). (Refer to Table 18.) The risk of bleeding at the highest dose of aspirin with placebo was higher than the risk of bleeding with clopidogrel and the lowest aspirin dose.

In CURE,[12] there was no significant excess of major bleeding after coronary artery bypass grafting (CABG) in the clopidogrel group compared to the placebo group (1.3% vs. 1.1%; RR 1.26, 95% CI 0.93-1.71). Most of the patients scheduled for CABG discontinued the study medication 5 days (mean) before the procedure. The subset of patients (n=912) discontinuing clopidogrel within 5 days before CABG surgery had more major bleeding than the aspirin group (9.6% vs. 6.3%; RR 1.53, p=0.06).

Table 18. CURE:[12 23] Percentage of major and life-threatening bleeding per aspirin dose

Bleeding complications	ASA	ASA + Clopidogrel	All patients
*Major**			
ASA ≤ 100 mg (n=5320)	1.86	2.97	2.41
ASA 101-199 mg (n=3109)	2.82	3.41	3.12
ASA ≥ 200 mg (n=4110)	3.67	4.86	4.26
p-value for trend	<0.0001	<0.001	<0.0001
*Life-threatening***			
ASA ≤ 100 mg (n=5320)	1.26	1.75	1.50
ASA 101-199 mg (n=3109)	1.90	1.39	1.64
ASA ≥ 200 mg (n=4110)	2.37	3.29	2.82
p-value for trend	0.004	0.0006	<0.0001

*Major bleeding defined as substantially disabling bleeding, intraocular bleeding leading to loss of vision or bleeding necessitating blood transfusion of 2 or more units of blood. **Life-threatening bleeding: fatal or leading to a reduction in the hemoglobin level of at least 5 g/dl, significant hypotension with need for inotropes, requiring surgical intervention, symptomatic intracranial hemorrhage or requiring blood transfusion of 4 or more units.

In the PCI-CURE[15] trial, no difference in major or minor bleeding was seen between clopidogrel and placebo at 30 days. At the end of follow-up (mean 8 months), the only statistically significant difference in bleeding for clopidogrel compared to placebo was in minor bleeding episodes (RR 1.68, 95% CI 1.06-2.68, p=0.03).

In the ARMYDA-2[17] trial, secondary endpoints included the occurrence of any vascular/hemorrhagic complications including major bleeding, minor bleeding, entry-site complications (hematoma, pseudoaneurysm, or ateriovenous fistula); and thrombocytopenia with platelet count $<70x10^9$/L or side effects requiring clopidogrel discontinuation. No patient in either clopidogrel group experienced post-procedural major bleeding or required transfusions. Post-procedural thrombocytopenia or significant side effects requiring interruption of clopidogrel were not observed in either group. Minor bleeding occurred in one patient in the 600 mg group; (gingival bleeding during glycoprotein IIb/IIIa infusion) and one patient in the 300 mg group; (urethral bleeding). A groin hematoma developed in 9 and 6 patients in the 600 mg and 300 mg group, (p=0.56), respectively. These minor bleeding episodes did not result in any local vascular complications that required surgery. The authors noted that the sample size was calculated on assumptions related to any post-procedural increase of CK-MB levels, and not the primary endpoint. Although no significant complications were noted with the higher dose of clopidogrel, the study is underpowered regarding the primary endpoint and, possibly, the secondary safety endpoints.

In CHARISMA[13] trial, the rate of the primary safety endpoint (severe bleeding according to GUSTO definition) was 1.7% in the clopidogrel group and 1.3% in the placebo group (RR 1.25, 95% CI 0.97-1.61; p=0.09). The rate of moderate bleeding was 2.1% in the clopidogrel group, as compared with 1.3% in the placebo group (RR 1.62, 95% CI 1.27-2.08; p<0.001). The incidence of intracranial hemorrhage did not differ between the two treatment groups. (See Table 19.) The rates of severe bleeding among the asymptomatic subgroup patients were 2.0% with clopidogrel and 1.2% with placebo; p=0.07; and the corresponding rates among symptomatic

subgroup patients were 1.6% and 1.4%; p=0.39, respectively. The rates of moderate bleeding among the asymptomatic patients increased but remained nonsignificant (2.2% with clopidogrel and 1.4% with placebo; p=0.08). The difference in the rate of moderate bleeding in the symptomatic subgroup patients did reach significance, 2.1% with clopidogrel and 1.3% with placebo, p<0.001.

Table 19. CHARISMA[13] Trial: Safety Endpoints

Safety endpoints	C + ASA (n=7802)	P + ASA (n=7801)	RR (95% CI)	P value
Severe bleeding*	130 (1.7)	104 (1.3)	1.25 (0.97-1.61)	0.09
Fatal bleeding	26 (0.3)	17 (0.2)	1.53 (0.83-2.82)	0.17
Primary intracranial hemorrhage	26 (0.3)	27 (0.3)	0.96 (0.56-1.65)	0.89
Moderate bleeding**	164 (2.1)	101 (1.3)	1.62 (1.27-2.08)	<0.001

C=clopidogrel; ASA=aspirin; P=placebo; CI denotes confidence interval; *fatal bleeding and intracranial hemorrhage, or bleeding that caused hemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention); ** bleeding that led to transfusion but did not meet the criteria for severe bleeding.

In CAPRIE[22 60] trial, rash and GI hemorrhage differed significantly by treatment group. More aspirin than clopidogrel patients experienced severe GI hemorrhage (0.71% vs. 0.49%; p=0.05), whereas more clopidogrel than aspirin patients experienced severe rash (0.26% vs. 0.10%; p=0.017). The frequency of intracranial hemorrhage (0.4% vs. 0.5%) and indigestion/nausea/vomiting (1.2% vs. 0.97%) was higher with aspirin than clopidogrel, but not significantly so. The frequency of diarrhea was higher with clopidogrel than aspirin, though not significantly so (4.5% vs. 3.5%; p=0.056).

A randomized study[46] compared the antiplatelet effects after stent implantation in 61 patients using three different treatment arms over 2 weeks: Group A (ticlopidine 500 mg plus ASA 300 mg per day); Group B (ticlopidine 500 mg monotherapy); or Group C (ASA 300 mg per day). One major bleeding event occurred in one patient from Group C, with that patient's hemoglobin dropping by 4 mg/dL due to a groin hemorrhage. No blood transfusion was required.

In the ESPS-2[57] trial, 430/6602 patients reported at least one adverse bleeding event during the 2-year follow-up period. Most patients 279/430 (64.9%) were treated with aspirin but 151/430 (35.1%) were either on placebo or ERDP alone. Of all the bleeding complications, 370 (86%) were mild to moderate, while the remaining 60 cases (14%) were considered severe enough to require blood transfusion or were fatal. In the sixty patients with severe bleeding, 47/60 were on aspirin and of those, 27/47 were in the ASA/ERDP group. (Refer to Table 20 for the pair-wise comparison of bleeding complications.)

Table 20.* Incidence of Bleeding Complications in ESPS-2

Bleeding Complication	ERDP (%)	ERDP/ASA (%)	ASA (%)	RR (94% CI)	P value
ERDP vs. ASA					
Any site	4.7	-	8.2	0.57 (0.43 – 0.75)	<0.001
Mild	3.2	-	5.0	0.64 (0.46 – 0.90)	0.010
Moderate	1.1	-	2.0	0.54 (0.31 – 0.96)	0.033
Severe or fatal	0.4	-	1.2	0.30 (0.12 – 0.74)	0.006
ERDP/ASA vs. ASA					
Any site	-	8.7	60.0	1.07 (0.85 – 1.33)	0.577
Mild	-	5.1	30.4	1.02 (0.76 – 1.38)	0.877
Moderate	-	2.0	29.2	1.00 (0.62 – 1.61)	0.998
Severe or fatal	-	1.6	33.1	1.35 (0.76 – 2.40)	0.305
ERDP/ASA vs. ERDP					
Any site	4.7	8.7	-	1.87 (1.43 – 2.45)	<0.001
Mild	3.2	5.1	-	1.59 (1.13 – 2.23)	0.007
Moderate	1.1	2.0	-	1.84 (1.04 – 3.25)	0.034
Severe or fatal	0.4	1.6	-	4.51 (1.87 – 10.90)	<0.001

*Adapted from Jones et al.[34]; ERDP = Extended-release dipyridamole; ASA = aspirin.

In the ESPRIT[21] trial, major bleeding complication occurred in 35/1363 (2.6%) and 53/1376 (3.9%) in the extended-release dypridamole-ASA patients compared to the aspirin group, RR 0.67, (95% CI 0.44-1.03). There were 3 patients in the combined group that experienced fatal intracranial bleeding vs. 4 patients in the aspirin group. Nine patients had non-fatal intracranial bleed in the extended-release dypridamole-ASA group vs. 17 in the aspirin group. Minor bleeding was reported in 171 patients taking the combined regimen vs.168 patients on aspirin alone; RR 1.03, 95% CI 0.84-1.25.

In the MATCH[19] trial, adding aspirin to clopidogrel resulted in significantly more bleeding complications compared to clopidogrel alone. Life-threatening bleeding, including symptomatic intracranial hemorrhage occurred more frequently in patients randomized to aspirin and clopidogrel compared to clopidogrel alone (2.6% vs. 1.3%; p<0.0001; absolute risk increase 1.3% (95% CI 0.6-1.9). Gastrointestinal bleeds were the most common cause of the life-threatening bleeds, 1.4% with clopidogrel and ASA vs. 0.6% with clopidogrel alone. No significant increase in fatal bleeding was observed between the two groups. Major bleeding defined as disabling bleeding, intra-ocular bleeding leading to the loss of vision or needing blood transfusion of ≤ 3 units of blood occurred more often with clopidogrel plus ASA compared to clopidogrel alone (1.9% vs. 0.6%; p <0.0001). Minor bleeding was also higher in patients who were allocated clopidogrel plus ASA compared to those who received clopidogrel alone (3.2% vs. 1.0%; p<0.0001).

In the TASS[20] trial, bleeding events including minor symptoms (easy bruising, petechiae, epistaxis and microscopic hematuria) and serious hemorrhages, such as GI bleeding were reported. Nine percent of the patients taking ticlopidine and 10% of those treated with aspirin reported some evidence of bleeding during the trial although about half of the events were

thought to be unrelated to the study medication. The events most frequently reported were purpura and epistaxis.

In Leon et al.[47] study, hemorrhagic and vascular surgical complications were significantly different among the three antithrombotic drug regimens. More specifically, hemorrhagic complications (not defined) occurred more commonly with ticlopidine and aspirin than with aspirin alone (RR 3.06; p=0.002).

A recent randomized, double-blind trial[27] evaluated whether high-risk patients (n=320, mean age, 72 years) presenting with a upper GI bleed on ≤ 325 mg of ASA would have fewer subsequent bleeding episodes on clopidogrel 75 mg or aspirin 80 mg plus esomeprazole (proton pump inhibitor) after endoscopically confirmed ulcer healing had taken place at 8 weeks. The primary endpoint was recurrent ulcer bleeding and the duration of the study was 12 months. *H. pylori* positive patients and/or those taking any medications that increased the risk of bleeding (NSAIDs or anticoagulants) were excluded. At 12 months, the likelihood of recurrent ulcer bleeding and lower GI bleeding with clopidogrel was 8.6% (95% CI 4.1-13.1), but with low-dose aspirin and esomeprazole it was 0.7% (95% CI 0-2.0), giving an absolute difference of 7.9% (95% CI 3.4-12.4; p = 0.001).

Risk of Bleeding

In the ESPS-2[57] trial, of the 430 reported bleeding in the study, 271 (63%) were mild (mostly epistaxis or bruising), requiring no medical treatment. In this category of bleeding complications, the incidence in the ASA groups was 60% higher than in the two groups not treated with ASA, while the incidence of bleeding in the ERDP only arm was identical to that in the placebo arm. Since bleeding occurred equally in patients treated with ASA alone and ERDP/ASA combined, it is concluded that ERDP does not predispose to spontaneous bleeding from any site.

Serebruany et al.[73] evaluated the risk of bleeding complications with antiplatelet agents in a meta-analysis (n=50 trials, n=338,191 patients). There were ten thienopyridine trials (eight for ticlopidine, three for clopidogrel), which included 21,582 patients. (One trial compared two thienopyridines head-to-head; one trial of ERDP/ASA was included, as were six trials with ASA <100 mg and 20 trials with ASA ≥ 100 mg). Despite substantial differences in the way patterns of bleeding complications were reported, low-dose aspirin and dipyridamole therapy had the lowest risk of bleeding (3.6% and 6.7%, respectively). The trials including ASA in doses greater than 100 mg had similar rates of hemorrhagic events compared with the thienopyridines. (Refer to Table 21.)

Table 21. Meta-analysis:[73] Frequency of bleeding complications per antiplatelet class and dose

Bleeding type	No. of trials reported	No. of patients	% Rate (95% CI)
Major bleeding			
ASA <100 mg	5	13,337	1.7 (1.4-1.9)
ASA 100-325 mg	11	43,489	1.7 (1.5-1.8)
ASA >325 mg	2	1,409	2.5 (1.7-3.3)
Dipyridamole*	2	3,304	1.0 (0.7-1.3)
Thienopyridines	8	18,574	2.1 (1.9-2.3)
Minor bleeding			
ASA <100 mg	3	11,963	1.8 (1.5-2.0)
ASA 100-325 mg	5	13,588	6.5 (6.1-6.9)
ASA >325 mg	0		
Thienopyridines	1	6,259	5.1 (4.6-5.7)
Hemorrhagic bleed			
ASA <100 mg	4	12,661	0.3 (0.2-0.4)
ASA 100-325 mg	15	152,955	0.3 (0.2-0.3)
ASA >325 mg	3	2,224	1.1 (0.7-1.5)
Thienopyridines	2	15,858	0.3 (0.2-0.3)
GI bleed			
ASA <100 mg	5	13,337	1.1 (0.9-1.3)
ASA 100-325 mg	7	30,413	2.4 (2.2-2.6)
ASA >325 mg	3	2,224	2.5 (1.8-3.1)
Thienopyridines	5	17,824	1.6 (1.4-1.8)
TOTAL			
ASA <100 mg	4	12,639	3.6 (3.3-3.9)
ASA 100-325 mg	6	22,745	9.1 (8.7-9.4)
ASA >325 mg	1	1,540	9.9 (8.4-11.4)
Dipyridamole*	2	3,304	6.7 (5.8-7.5)
Clopidogrel	7	19,191	8.5 (8.1-8.8)

*Extended-Release Dipyridamole and Extended-Release Dipyridamole + ASA combined.

Specific Adverse Events or Withdrawal due to Specific Adverse Events (GI, Increase bleeding, neutropenia, rash)

Neutropenia

Infrequent but important hematological adverse effects of ticlopidine include neutropenia, agranulocytosis, aplastic anemia, pancytopenia, thrombotic thrombocytopenic purpura, and thrombocytopenia. One review article,[74] not included in this review due to inappropriate design, showed that by 1994, ticlopidine was associated with 645 cases (16% fatal) of aplastic anemia, bone marrow suppression, pancytopenia, or agranulocytosis worldwide. The total number of persons exposed to the drug during this period is unknown and hence incidence cannot be precise. Women ≥ 75 years old who took ticlopidine appeared to develop these hematological disorders more often.

In the TASS[20] study, 35 of 1518 (2.3%) developed neutropenia (ANC < 1.2 x 10^9/L), while 13 (0.9%) developed severe but reversible, neutropenia with an ANC <0.45 x 10^9 while taking ticlopidine. In general, severe neutropenia usually developed between 1 and 3 months after ticlopidine therapy was initiated, and resolved within 3 weeks of discontinuation.

In the CATS[68] trial, using the same definition of neutropenia and severe neutropenia as in the TASS[20] study, ticlopidine was associated with neutropenia in 11/525 (2%) of patients, of

which four cases (0.8%) were severe. All cases occurred during the first three months of therapy but resolved when ticlopidine was discontinued. No clinical complications or deaths were reported. The CATS[68] trial was not included in the current review because ticlopidine was not compared to aspirin or another drug of interest. Even so, combined data from CATS[68] and TASS[20] suggests a 2.4% incidence for neutropenia and a 0.85% incidence for severe neutropenia and agranulocytosis with ticlopidine.[74]

In contrast, in STARS[75] and ISAR,[76] two large phase 3 clinical trials in the setting of PCI (not included in this drug review because the comparator drug was placebo or an anticoagulant agent), found no difference in rates of neutropenia between ticlopidine and control groups during the first month of observation (0.5% vs. 0% in ISAR and 0.2% for all patients enrolled in STARS). No cases of thrombotic thrombocytopenic purpura (TTP) were reported in these phase 3 trials. (Refer below for further discussion on TTP.)

In CAPRIE,[60] severe neutropenia with clopidogrel was observed in six patients: four on clopidogrel, two on aspirin. Two clopidogrel patients and one aspirin patient had neutrophil counts of zero. One patient taking clopidogrel was receiving cytotoxic chemotherapy.

In CURE,[12] the rates of neutropenia (3 on clopidogrel plus aspirin vs. 3 on aspirin alone) and thrombocytopenia (19 clopidogrel plus aspirin vs. 24 aspirin alone) were similar.[10] No cases of TTP were reported.

The study by Leon et al.[47] found that rates of neutropenia or thrombocytopenia for aspirin and ticlopidine were 0.5%, with incidences of 0.2% for aspirin, and 0.2% for aspirin and warfarin (RR 3.06, 95% CI 0.36-26.2, p=0.74).

In summary, neutropenia may occur with ticlopidine in up to 2.4% of patients, with 0.85% of these having severe neutropenia or agranulocytosis. As a reference point, this would be slightly less than the incidence of agranulocytosis with clozapine (estimated incidence, 1–2%). The incidence of neutropenia with clopidogrel is similar to that with aspirin.

Thrombocytopenia and thrombotic thrombocytopenic purpura (TTP)

Thrombocytopenia and thrombotic thrombocytopenic purpura (TTP) are rare occurrences with the thienopyridines. TTP was never reported in the major clinical trials with ticlopidine, although case reports began to appear about 7 years after the Food and Drug Administration approved it.[74] Between the years of 1992 and 1997, 119 cases of ticlopidine-induced TTP were reported to the FDA MedWatch Program.[77] Typically, ticlopidine-induced TTP occurs 2 to 12 weeks after treatment is initiated.

Based on available evidence, the estimated incidence of TTP ranges from about 1 case per 1600 to 5000,[78] with a mortality rate of 33%.[79]

In CHARISMA trial,[13] there was one documented nonfatal case of TTP in the clopidogrel-treated group.

Bennett et al.[79] evaluated whether the incidence of TTP differed in patients undergoing stent placement (mean age 62.4 ± 11.5, n=42) compared to those who had had a stroke (mean age 62.4 ± 11.5, n=56). In the comparison, no difference in TTP mortality was seen (37.5% vs. 28.6; p >.05). Among patients with TTP, the highest mortality was seen in patients who did not receive timely therapeutic plasmapheresis (57.9% vs. 18.3%; p<.001).

In a later study, Bennett et al.[78] reported 11 cases of TTP with clopidogrel, 6 of those in women. Persons affected ranged in age from 35 to 70 years old (median, 55 years old).

Thrombotic thrombocytopenic purpura occurred within 3 to 14 days in all but one patient, and one patient had discontinued clopidogrel 3 weeks prior to the onset of TTP. As part of the

worldwide postmarketing surveillance for clopidogrel, suspected cases of TTP have been reported at a rate of about 4 cases per million exposed.[10]

Meta-analysis of Specific Adverse Events: Comparison with Aspirin

The patient-level adverse event analysis included 18 trials and evaluated 15 types of specific adverse events (minor bleeding, major bleeding, non-specific bleeding, thrombocytopenia, leucopenia/neutropenia, other hematological, liver, other gastrointestinal, metabolic/endocrinologic, central nervous system, and rash, cardiovascular or other non-specified vascular events, psychiatric, musculoskeletal, and urologic). The results of our meta-analysis of specific adverse events at a patient level are shown in Tables 22, 23, and 24.

Table 22 presents our statistical analysis of the trials that compared study antiplatelet agents with aspirin. Some events are rare and 95% confidence intervals are wide, making it difficult to draw strong conclusions about the relative difference in adverse events between therapies. However, some findings are worth noting. Clopidogrel was associated with more major and minor bleeding than aspirin, and ticlopidine was associated with more leukopenia/neutropenia than aspirin. Both ticlopidine and clopidogrel were associated with rash more than aspirin, and there were associations of lesser strength between ticlopidine and other GI events and dipyridamole plus aspirin and CNS events.

Table 22. Patient Adverse Event Analysis: Antiplatelet Agents vs. Aspirin

			Aspirin		Intervention Groups			
Adverse Events	Drug	# of trials	# people with event	sample size	# people with event	sample size	Pooled OR	95% CI
Minor Bleeding	Clopidogrel	1	153	6303	322	6259	2.18	(1.79, 2.67)
Minor Bleeding	Clopidogrel + Aspirin	2	160	8864	220	8855	1.39	(1.13, 1.72)
Minor Bleeding	Dipyridamole	0	NR	NR	NR	NR	NC	NC
Minor Bleeding	Dipyridamole + Aspirin	1	168	1376	171	1363	1.03	(0.82, 1.30)
Minor Bleeding	Ticlopidine	1	2	131	0	92	0.00	(0.0, 55.11)
Major Bleeding	Clopidogrel	2	584	15889	592	15858	1.02	(0.90, 1.14)
Major Bleeding	Clopidogrel + Aspirin	2	202	8864	250	8855	1.25	(1.03, 1.52)
Major Bleeding	Dipyridamole	0	NR	NR	NR	NR	NC	NC
Major Bleeding	Dipyridamole + Aspirin	1	53	1376	35	1363	0.66	(0.41, 1.03)
Major Bleeding	Ticlopidine	2	29	2434	11	2420	0.38	(0.17, 0.78)
Non-specified Bleeding	Clopidogrel	1	890	9586	890	9599	1.00	(0.90, 1.10)
Non-specified Bleeding	Dipyridamole	0	NR	NR	NR	NR	NC	NC
Non-specified Bleeding	Dipyridamole + Aspirin	1	135	1649	144	1650	1.07	(0.83, 1.38)
Non-specified Bleeding	Ticlopidine	2	163	2434	143	2420	0.87	(0.68, 1.11)
Non-specified Bleeding	Ticlopidine + Aspirin	1	10	557	30	546	3.18	(1.49, 7.36)
Thrombocytopenia	Clopidogrel	1	28	6303	26	6259	0.93	(0.53, 1.66)
Thrombocytopenia	Dipyridamole	0	NR	NR	NR	NR	NC	NC
Thrombocytopenia	Ticlopidine	1	2	907	3	902	1.51	(0.17, 18.11)
Leukopenia/Neutropenia	Clopidogrel	1	5	6303	8	6259	1.61	(0.46, 6.27)
Leukopenia/Neutropenia	Dipyridamole	0	NR	NR	NR	NR	NC	NC
Leukopenia/Neutropenia	Ticlopidine	2	8	2434	44	2420	5.66	(2.63, 13.98)
Leukopenia/Neutropenia	Ticlopidine + Aspirin	2	1	660	4	669	3.94	(0.39, 194.64)
Other Hematological	Clopidogrel	0	NR	NR	NR	NR	NC	NC
Other Hematological	Dipyridamole	0	NR	NR	NR	NR	NC	NC
Other Hematological	Ticlopidine	1	29	907	38	902	1.33	(0.79, 2.26)
Liver	Clopidogrel	1	302	9586	285	9599	0.94	(0.80, 1.11)
Liver	Dipyridamole	0	NR	NR	NR	NR	NC	NC

			Aspirin		Intervention Groups			
Adverse Events	Drug	# of trials	# people with event	sample size	# people with event	sample size	Pooled OR	95% CI
Liver	Ticlopidine	0	NR	NR	NR	NR	NC	NC
Other GI	Clopidogrel	1	2008	9586	1869	9599	0.91	(0.85, 0.98)
Other GI	Dipyridamole + Aspirin	1	1433	1649	1650	1650	NC	NC
Other GI	Ticlopidine	3	793	2565	860	2512	1.19	(1.04, 1.37)
Metabolic Endo	Clopidogrel	0	NR	NR	NR	NR	NC	NC
Metabolic Endo	Dipyridamole	0	NR	NR	NR	NR	NC	NC
Metabolic Endo	Ticlopidine	1	10	907	11	902	1.11	(0.42, 2.92)
CNS	Clopidogrel	0	NR	NR	NR	NR	NC	NC
CNS	Dipyridamole + Aspirin	1	1027	1649	1116	1650	1.27	(1.09, 1.46)
CNS	Ticlopidine	1	60	907	66	902	1.11	(0.76, 1.63)
CNS	Ticlopidine + Aspirin	1	2	557	0	546	0.00	(0, 5.43)
Rash	Clopidogrel	1	442	9586	578	9599	1.33	(1.17, 1.51)
Rash	Dipyridamole + Aspirin	0	NR	NR	NR	NR	NC	NC
Rash	Ticlopidine	2	100	2434	225	2420	2.44	(1.90, 3.15)
Rash	Ticlopidine + Aspirin	1	0	103	2	123	+Inf	(0.16, +Inf)
Cardiovascular or other non-specified vascular event	Clopidogrel	0	NR	NR	NR	NR	NC	NC
Cardiovascular or other non-specified vascular event	Dipyridamole	0	NR	NR	NR	NR	NC	NC
Cardiovascular or other non-specified vascular event	Ticlopidine	1	76	907	66	902	0.86	(0.60, 1.23)
Cardiovascular or other non-specified vascular event	Ticlopidine + Aspirin	2	11	669	3	660	3.74	(0.98, 20.96)
Psych	Clopidogrel	0	NR	NR	NR	NR	NC	NC
Psych	Dipyridamole	0	NR	NR	NR	NR	NC	NC
Psych	Ticlopidine	1	5	907	10	902	2.02	(0.63, 7.57)
Musculoskeletal	Clopidogrel	0	NR	NR	NR	NR	NC	NC
Musculoskeletal	Dipyridamole	0	NR	NR	NR	NR	NC	NC
Musculoskeletal	Ticlopidine	1	11	907	17	902	1.56	(0.69, 3.72)
Urological	Clopidogrel	0	NR	NR	NR	NR	NC	NC
Urological	Dipyridamole	0	NR	NR	NR	NR	NC	NC

			Aspirin		Intervention Groups			
Adverse Events	Drug	# of trials	# people with event	sample size	# people with event	sample size	Pooled OR	95% CI
Urological	Ticlopidine	1	17	907	24	902	1.43	(0.73, 2.86)
Other	Clopidogrel	0	NR	NR	NR	NR	NC	NC
Other	Dipyridamole	0	NR	NR	NR	NR	NC	NC
Other	Ticlopidine	1	43	907	41	902	0.96	(0.60, 1.52)

NR, Not Reported; NC, Not Calculated; CI, Confidence interval; OR, Odds ratio.

In Table 23, trials comparing ticlopidine to clopidogrel are summarized. Ticlopidine had significantly more other GI and rash events than clopidogrel.

Table 23. Patient Adverse Event Analysis: Ticlopidine vs. Clopidogrel

		Ticlopidine		Clopidogrel			
Adverse Events	# of trials	# people with event	sample size	# people with event	sample size	Pooled OR	95% CI
Major Bleeding	1	4	340	9	680	1.13	(0.31, 5.04)
Non-specified Bleeding	2	2	597	2	577	1.06	(0.01, 83.12)
Thrombocytopenia	3	3	1202	13	1854	4.36	(0.95, 40.78)
Leukopenia/Neutropenia	3	4	1202	0	1854	0.00	(0.0, 1.52)
Other GI	3	20	1202	18	1854	0.48	(0.23, 0.97)
Rash	3	31	1202	11	1854	0.17	(0.07, 0.36)

OR, Odds Ratio; CI, Confidence interval.

Finally, Table 24 presents the summary of adverse events of trials comparing ticlopidine and aspirin to clopidogrel and aspirin. As with Table 23, ticlopidine with aspirin had more other GI and rash events than clopidogrel with aspirin.

Table 24. Patient Adverse Event Analysis: Ticlopidine + Aspirin vs. Clopidogrel + Aspirin

		Ticlopidine + Aspirin		Clopidogrel + Aspirin			
Adverse Events	# of trials	# people with event	sample size	# people with event	sample size	Pooled OR	95% CI
Minor bleeding	2	6	245	8	251	1.31	(0.39, 4.65)
Major bleeding	2	3	245	4	251	1.24	(0.21, 8.60)
Non-specified bleeding	1	1	153	2	154	2.00	(0.10, 118.75)
Leukopenia/Neutropenia	2	7	1735	0	636	0.00	(0, 1.41)
Liver comparison	1	1	345	0	355	0.00	(0, 37.90)
Other GI	4	78	2102	14	1004	0.50	(0.25, 0.92)
Rash	5	102	2133	13	1041	0.34	(0.17, 0.63)
Cardiovascular or other non-specified vascular event	1	2	153	2	154	0.99	(0.07, 13.87)
Other	2	26	499	10	509	0.36	(0.15, 0.79)

OR= Odds Ratio; CI =Confidence interval; Inf = Infinity.

Key Question 3. Safety and Efficacy: Patient Subgroups

Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), or co-morbidities (drug-disease interactions) or pregnancy for which one antiplatelet agent is more effective or associated with fewer adverse effects?

Age

There were no head-to-head trials or active-controlled trials that specifically compared the safety or effectiveness of the newer antiplatelet agents by age. In various analyses, however, age did not affect the overall tolerability or efficacy of these agents. In a subset analysis of CURE,[12] clopidogrel plus aspirin showed benefit in the rates of the first primary outcome in patients > 65 years old (13.3% vs. 15.3%), as it did in those ≤ 65 years old (5.4% vs. 7.6%) compared to placebo plus aspirin..

According to the manufacturer, clopidogrel plasma concentration of the main circulating metabolite are higher in older (≥ 75 years) than in younger healthy volunteers, but the higher plasma levels do not appear to correlate with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.[10]

A separate analysis of the ESPS-2[80] trial was performed for three 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, ERDP/ASA 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.

One case-control study[81] 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 (Refer to the Adverse Event Quality Table A2), 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 GI bleeding risks when using GI protectants, NSAIDS, or corticosteroids) users of ticlopidine showed an increased risk of hospitalization for bleeding episodes compared to nonusers of ticlopidine (OR 1.07, 95% CI 0.86-1.34). For comparison, the adjusted rate of hospitalizations for aspirin users due to bleeding was (OR 1.07, 95% CI 0.96-1.18).

Racial Groups

There is little evidence to suggest that the newer antiplatelet drugs differ in effect or tolerance across ethnic groups. One study[54] 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, MI 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 TTP.

Gender

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 subset analysis[12] of the CURE trial showed no difference in the rates of the first primary outcome among men on clopidogrel and aspirin and men taking aspirin and placebo (9.1 vs. 11.9). A similar finding for the first primary outcome was noted for women (9.5% vs. 10.7%).

A prospectively defined subgroup analysis for gender (29.8% female) in the CHARISMA[13] trial suggested no substantial benefit of using clopidogrel for MI, stroke, or death from cardiovascular causes in women[13 31] though the reason for this finding, and the extent to which it is true, remains unclear. Further studies in this regard are required before a conclusion can be reached.

No significant difference was observed in the plasma level of the main circulating metabolite of clopidogrel between males and females.[10] In a small study, less inhibition of ADP-induced platelet aggregation was observed in women than men but with no observed difference in prolongation of bleeding time.

In TASS,[20] 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[18] trial, 42% of the study population was women. No gender difference in efficacy or tolerability was noted.

Comorbidities

In a subset analysis[12] of CURE, patients with diabetes had a lower incidence of the first primary outcome on clopidogrel plus ASA than placebo plus ASA (14.2% vs.16.7 % , respectively). Likewise, patients without diabetes also had a lower incidence of the first primary outcome with clopidogrel plus ASA than placebo plus ASA (7.9 to 9.9%, respecitvely). Patients with diabetes had higher event rates than non-diabetics but within the diabetic group, those on clopidogrel plus ASA showed a benefit compared to placebo plus ASA.

In several prespecified subgroup analyses using the primary endpoint in the CHARISMA[13] trial, patients with and without a history of diabetes, hypertension, hypercholesterolemia, stroke, prior CABG or PCI, 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 MI or CABG and patients with ≥ 30 body-mass index fared better with clopidogrel plus ASA than ASA 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.[31] 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.

The CAPRIE[22] trial was not powered to detect overall differences between patient subgroups. As mentioned earlier, while a statistical analysis suggested heterogeneity, the reason for that finding, and the extent to which it influences apparent benefit, remains unclear. The pre-planned subgroup analyses should be viewed with caution. One pre-planned subgroup analysis found that PVD patients had significant benefit with clopidogrel over aspirin in regards to the primary outcome (3.71% vs. 4.86%; RRR 23.8%, p=0.0028). (Refer to Table 25.)

Table 25. Results of CAPRIE:[22] Treatment Effect on Outcome by Subgroup

Patient subgroup	No. of events Pt-years at risk		RRR (95%CI), p	ARR,%
	Clopidogrel	ASA		
Ischemic stroke	433/6054	461/5979	7.3 (-5.7 to 18.7), 0.26	0.56
MI	291/5787	283/5843	-3.7 (-22.1 to 12.0),0.66	-0.19
PAD	215/5795	277/5797	23.8 (8.9 to 36.2),0.0028	1.15
All patients§	939/17636	1021/17519	8.7 (0.3 to 16.5),0.043	0.51

§ The test of heterogeneity for the RR across the three subtypes was significant at p=.04, suggesting that the benefit of clopidogrel may not be identical across the subgroups.

A CAPRIE cohort analysis[82] in patients with ischemic stroke (IS) or MI reported a lower event rate in the primary and secondary endpoints compared to the overall CAPRIE population. The NNT for the prevention of one ischemic event (IS, MI, or vascular death) in the overall CAPRIE cohort was 196 patients per year of treatment with clopidogrel instead of ASA compared with 71 in those patients with preexisting IS or MI. At 3 years, to prevent one ischemic event, the NNT would be 29 for the patients in the IS or MI cohort compared to 91 in the overall CAPRIE population. Comparable reductions in the NNT were also seen for the secondary endpoint (IS, MI, or rehospitalization).

An observational cohort study called the CAPRIE Actual Practice Rates Analysis (CAPRA)[83] suggested the 8.7% RRR observed in the CAPRIE study for the combined risk of ischemic stroke, MI, or vascular death might not be applicable to different populations with different disease prevalence. However, this was not an actual intervention trial and any conclusion must be viewed with caution.

Using CAPRIE data, a multivariate analysis[84] demonstrated a significant RRR for various individual and composite endpoints with clopidogrel in a subset of patients with history of a previous cardiac surgery. The composite endpoint of vascular death, MI or ischemic stroke resulted in a 36.3% reduction (95% CI 13.4-53.1) with clopidogrel (5.8% event rate per year) compared with aspirin (9.1% even rate per year; p=0.004). Similarly, there was a 31.8% RRR in all-cause death, MI, or all-cause stroke (95% CI 8.2-49.4; p=0.011). The percentage of patients hospitalized for any bleeding event was 1.4% in the clopidogrel group compared to 2% for patients on ASA (RRR 28.5%, 95% CI -56.4-67.3; p=0.398). In a multivariate model incorporating baseline clinical characteristics, clopidogrel therapy was independently associated with a decrease in vascular death, MI, stroke, or rehospitalization in patients with a history of cardiac surgery, with a 31.2% RRR (95% CI 15.8-43.8; p=0.003).

Another CAPRIE multivariate analysis[62] demonstrated that the development of fatal or nonfatal MI over a 3-year period could be predicted on the basis of baseline characteristics of the patients enrolled in the CAPRIE study. Clopidogrel was associated with a 19.2% RRR for the development of AMI over a 3-year period, (p=0.008).

In ESPS-2, additional subanalyses[9] reportedly showed that the benefit in stroke reduction was found in patients with varying comorbidities. Analyses were conducted for those with specified baseline comorbidities (IHD, DM, and PVD) and the primary endpoints. In that regard, unpublished results using drug-disease interaction analyses suggested that, as in the main study, a benefit in prevention of first stroke (fatal and nonfatal) was seen with combination ERDP/ASA (Refer to Table 26.) However, comparative statistics within subgroups were not provided.

Table 26. ESPS-2 trial:[9] Outcome data for first stroke (fatal or non-fatal) in patients with IHD, PVD, NIDDM and IDDM

	Aggrenox	ERDP	ASA	Placebo
Number of patients enrolled	1650	1654	1649	1649
# Pts with a hx of IHD at baseline (%)	573 (34.7)	598 (36.2)	571 (34.6)	577 (35)
# Pts with a stroke at 730 days (%)	72 (12.6)	99 (16.6)	89 (15.6)	109 (18.9)
% survival at 730 days* (95% CI)	86.4 (83.4, 89.3)	82.4 (79.2, 85.5)	83.5 (80.3, 86.6)	79.9 (76.5, 83.3)
# Pts with a hx of PVD at baseline (%)	358 (21.7)	371 (22.4)	362 (22.0)	363 (22.0)
# Pts with a stroke at 730 days (%)	34 (9.5)	54 (14.6)	57 (15.7)	77 (21.2)
% survival at 730 days* (95% CI)	89.7 (86.5, 93.0)	84.6 (80.8, 88.3)	83.2 (79.2, 87.2)	77.7 (77.3, 82.1)
# Pts with a hx of NIDDM at baseline (%)	204 (12.3)	229 (13.8)	182 (11.0)	186 (11.3)
# Pts with a stroke at 730 days (%)	24 (11.8)	39 (17.0)	27 (14.8)	39 (21.0)
% survival at 730 days* (95% CI)	87.5 (82.8, 92.2)	82.1 (77.0, 87.2)	84.8 (79.6, 90.1)	77.7 (71.6, 83.9)
# Pts with a hx of IDDM at baseline (%)	50 (0.03)	49 (0.03)	58 (0.04)	53 (0.03)
# Pts with a stroke at 730 days (%)	7 (14.0)	7 (14.3)	13 (22.4)	10 (18.9)
% survival at 730 days* (95% CI)	84.1 (73.2, 94.9)	84.5 (73.9, 95.1)	76.5 (65.3, 87.7)	80.4 (69.5, 91.4)

Hx= history; *Kaplan-Meier Estimate; IHD=Ischemic Heart Disease; NIDDM= non-insulin dependent diabetes mellitus; IDDM= insulin dependent diabetes mellitus.

A recent post-hoc analysis[70] 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 two models. Compared with aspirin alone, treatment with ERDP/ASA resulted in substantial relative hazard reductions (RHR) for stroke within some of the specific risk factor subgroups including those younger than 70 years of age, those with hypertension, prior MI, prior stroke or TIA, 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 TIA before the qualifying event. Those who already had at least 2 prior events (TIA/stroke), of which one was the qualifying events for inclusion into the study, had the least incidence of subsequent stroke compared to those who had only one prior event (the qualifying TIA/stroke). Patients with a history of MI who were treated with ERDP/ASA had a 36.8% RHR for stroke compared with those taking ASA alone. Patients with any prior CV disease had a 27.3% RHR while taking ERDP/ASA vs. 18.2% RHR in those that did not have a history of

prior CV disease. Patients taking ERDP/ASA had a greater RHR for the endpoint of combined stroke or vascular events among those patients with a prior stroke or TIAs, previous MI, and among current smokers. Sacco et al.[70] then conducted the analysis stratifying patients at low and high risk for recurrent stroke using the baseline ESPS-2 cohort which had been categorized according to the Framingham stroke risk score or the SPI-2 score as depicted in Table 27. 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 ERDP/ASA provides greater benefit for patients with a higher risk for stroke, as per predicted stroke probabilities.

Table 27.[70] Stroke or Vascular Event Rates in ESPS-2: ERDP/ASA or ASA Monotherapy

Risk Group	No. of Subjects	With ERDP/ASA*	With ASA* only	RHR, % (lower, Upper CL), %	P values
Annual Stroke Rates					
Framingham stroke risk score					
Low	1453	3.4	3.8	12.3 (-30.4, 41.0)	.52
High	1743	7.0	10.1	30.2 (10.3, 45.7)	.005
SPI-2 risk score					
Low	1426	3.2	3.7	11.8 (-32.9, 41.4)	.55
Moderate	1471	6.3	9.6	34.3 (12.8, 50.5)	.004
High	299	10.9	13.2	17.2 (-39.3, 50.8)	.48
Annual Stroke or Vascular Event Rates					
Framingham stroke risk score					
Low	1453	4.1	5.0	17.4 (-17.8, 42.1)	.29
High	1743	11.4	14.3	20.6 (2.7, 35.2)	.03
SPI-2 risk score					
Low	1426	4.2	4.9	13.8 (-23.3, 39.7)	.42
Moderate	1471	9.5	13.1	27.5 (8.1, 42.7)	.008
High	299	19.8	21.5	7.6 (-37.9, 38.1)	.70

Adapted from Sacco et al.[70]; * Data are given as annual percentage of subjects in each group who experienced a stroke.RHR = relative hazard reductions calculated using proportional hazards models; CL = confidence limit For Framingham Study model: the 10-year stroke probability (primarily first stroke) is low (≤0.15) or high (>0.15) using th 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 ye stroke for enrollment event, severe hypertension, and coronary artery disease.

Another post-hoc analysis[85] of the ESPS-2 trial evaluated whether aspirin, dipyridamole or the combination of the two agents was more efficacious in patients with well-defined previous cerebral ischemia associated with large vessel disease (LVD; n=1816) and small vessel disease (SVD; n=2600) during a mean follow-up of 1.7 years. The type of vessel disease was classified according to clinical symptoms or physical examination and not with imaging data. Signs and symptoms related to lacunar syndrome (pure motor stroke, pure sensory stroke, ataxic hemiparesis, or dysarthria clumsy hand syndrome) were considered SVD and any evidence of cortical dysfunction was classified as LVD. Examples of cortical syndrome would include dysphasia, dyspraxia, hemianopia, or a decreased level of consciousness at time of clinical examination. The primary outcome was the occurrence of the first vascular event. (e.g. nonfatal stroke, nonfatal myocardial infarction, a nonfatal other vascular event (deep venous thrombosis, pulmonary embolism, peripheral arterial occlusion, or venous retinal vascular events), or vascular death. A secondary outcome was the occurrence of a new stroke only. The hazard ratio

for the risk of a vascular event in patients who received combination of aspirin and dipyridamole vs. aspirin alone in patients with SVD and LVD were similar. The interaction was not significant in those patients with aspirin plus dipyridamole vs. aspirin for stroke in patients with SVD and LVD either. The findings of the study did not support the hypothesis that antiplatelet drugs are more effective in patients with LVD than in those with SVD.

The ESPRIT[21] trial conducted some planned subgroup analyses for the primary outcome event including age (≤ 65 years vs. > 65 years), sex, history of ischemic heart disease (previous MI or history of angina pectoris vs. no history of ischemic heart disease), type of cerebral ischemia (large vs. small vessel disease), and country (non-Asian vs. Asian). Subgroup analyses performed post-hoc were doses of aspirin <40 mg vs. 40-100 mg), and interval between event and randomization (<1 week vs. 1 week to 1 month vs. 1- 6 months). All subgroup analyses favored aspirin plus dipyridamole therapy vs. aspirin alone except in the subgroup that experienced the qualifying event less than 1 week prior to randomization. It is not clear what significance this has, if any, since the number of patients in that particular subgroup was small (two-thirds of the study population were randomized 1-6 months after the event).

Other Medications

There were no head-to-head trials or active-controlled trials that compared the safety or efficacy of newer antiplatelet agents when given with other concomitant medications. A hazard ratio analysis[30] demonstrated that the benefits of clopidogrel over ASA in reducing CV endpoints was consistent among those receiving, or not receiving, the following: heparin/LMWH; ASA; GP IIb/IIIa antagonist, beta-blockers, ACE inhibitors, lipid-lowering agents, calcium channel blockers and intravenous nitrates.

Pre-defined analyses of the primary endpoint from the CHARISMA[13] trial performed in several subgroups in patients including patients with prior use of other antiplatelet agents, angiotensin-converting-enzyme (ACE) inhibitors (overall and ramipril vs. other ACE inhibitors), statins (overall and atorvastatin, simvastatin, and pravastatin), beta-blockers, calcium antagonists, antidiabetic agents, angiotensin II-receptor blockers, cyclooxygenase-2 inhibitors, and anticoagulants were performed. Publication of the results was not included in the article. In the total population, 93.6% of patients were taking some antiplatelet agents within 10 days of study entry which included aspirin (92.7%), ticlopidine (0.6%), clopidogrel (3.5%) and dipyridamole (0.8%).[31]

A poster abstract[86] using CAPRIE data suggested that patients on various medications in the clopidogrel and ASA group experienced no differences in adverse events compared to the ASA group. These medications included ACE inhibitors, antidiabetics, anti-epileptics, beta-blockers, calcium channel blockers, coronary vasodilators, diuretics, peripheral vasodilators, lipid-lowering agents, and GPIIb/IIIa antagonist agents. There was no evidence that concurrent use of these drugs lead to different adverse consequences. However, all antiplatelet agents should be used cautiously with medications that increase the risk for bleeding. Likewise, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or coadministration with NSAIDs or warfarin.[10]

Per the package insert, ticlopidine should be used with caution in patients who may be at risk for increased bleeding from trauma, surgery, or pathological conditions.[87]

Dipyridamole (a component of ERDP/ASA) has a vasodilatory effect and should be used cautiously in patients with hypotension and severe coronary artery disease. It is unknown whether the dose of aspirin in ERDP/ASA provides adequate cardiac prophylaxis.[88]

In terms of drug interactions, clopidogrel in high concentrations inhibits the cytochrome P450 2C9 *in vitro*. Thus, clopidogrel may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and many NSAIDs. Information on specific drug interactions provided by the manufacturer[10] is summarized in Appendix E for clopidogrel.

Information from the literature provided by the manufacturer on specific drug interactions (since no drug-drug interaction studies have been conducted) for the individual components of ERDP/ASA is summarized in Appendix E.

A dossier for ticlopidine was not received from the manufacturer. Information for the drug-drug interactions are from the Ticlid® package insert and also depicted in Appendix E.

Pregnancy

Refer to Appendix F for the FDA definitions of the pregnancy categories. Clopidogrel and ticlopidine are Category B.[87 89] The components of Aggrenox® include dipyridamole, which is in Category B; aspirin is in Category D. Aggrenox® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Due to the aspirin component, Aggrenox® should be avoided in the third trimester of pregnancy.[88]

Table 28. Summary of the Evidence by Key Question

Key Question 1: Efficacy	Quality of Evidence	Conclusion
ACS: comparative efficacy on mortality (all-cause and CV), CV events (MI, stroke) invasive vascular procedure failure (including need for additional invasive vascular procedures)	Clopidogrel (good)	No head-to-head trials comparing the newer antiplatelet agents in ACS are available. No trials involving ticlopidine or extended-release dipyridamole/ ASA have been done in the setting of ACS. **Two active-controlled trials:** CURE trial: Clopidogrel plus ASA reduced all-cause/CV mortality (subgroup analysis) but not significantly compared to placebo plus ASA at 12 months, (mean duration 9 months). Clopidogrel in combination with ASA significantly reduced the first primary endpoint of death from CV causes, nonfatal MI or stroke at 12 months compared to placebo and ASA; (p<0.001). The combination of clopidogrel with ASA also reduced the second primary endpoint of death from CV causes, nonfatal MI, stroke or refractory ischemia, p<0.001. The incidence of MI for clopidogrel vs. placebo was 5.2% vs. 6.7%, p=0.001, NNT= 68 at 12 months. There was a risk reduction of 14% (NS) for stroke with clopidogrel compared to placebo at 12 months. There were fewer coronary revascularization procedures with clopidogrel compared to placebo at 12 months but a statistically significant difference was not seen. The study reported a 45% temporary and an ~20% permanent discontinuation rate of the study medications. The discontinutation rates due to adverse events were comparable between clopidogrel compared to placebo. CHARISMA trial: The primary endpoint, first occurrence of myocardial infarction, stroke (of any cause), or death from cardiovascular causes, (including hemorrhage) occurred in 6.8% with clopidogrel and 7.3% with placebo (RR, 0.93; 95% CI 0.83-1.05; p=0.22). The principal secondary efficacy endpoint, (first occurrence of MI, stroke, death from CV causes, or hospitalization for unstable angina, TIA, or a revascularization procedure) was 16.7% with clopidogrel and 17.9% with placebo (RR 0.93, 95% CI 0.87- 0.995; p=0.049). 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. A total of 4.8% patients taking clopidogrel and 4.9% of those in the placebo group discontinued treatment because of an adverse event; p=0.67.

Key Question 1: Efficacy	Quality of Evidence	Conclusion
Coronary Intervention Procedures: comparative efficacy on mortality (all-cause and CV), CV events (MI, stroke) invasive vascular procedure failure (including need for additional invasive vascular procedures)	Clopidogrel (good)	Eight head-to-head trials comparing clopidogrel vs. ticlopidine. Three trials were rated poor in quality, 4 trials were rated as fair and one trial (CLASSICS) was graded good in quality. No trials involving extended-release dipyridamole/ASA have been done in the setting of percutaneous coronary intervention (PCI). Six active controlled trials were evaluated. Two trials were rated poor. One trial was rated as fair. The other three trials (PCI-CURE, CREDO, and ARMYDA-2) were rated good in quality. **Head-to-Head trial:** CLASSICS trial: Clopidogrel (with and without loading dose) + ASA vs. Ticlopidine + ASA. This study was primarily a safety study. No difference was seen for major adverse clinical events (MI (fatal or non-fatal), target lesion revascularization, and sudden death) at 30 days between the two agents. **Clopidogrel: (three active-controlled trials):** PCI-CURE trial: Cardiovascular death from the time of the PCI to 30 days post PCI and from the time of the PCI to the end of follow-up (average duration, 8 months) was not statistically different with clopidogrel compared to placebo. The composite endpoint of cardiovascular death and MI before and after PCI was statistically significant, p =0.002 with clopidogrel compared to placebo at. The incidence of MI within 30 days following PCI was less with clopidogrel plus aspirin (2.1% vs. 3.8%) than placebo plus aspirin (RR 0.56, 95% CI 0.35-0.89, NNT=60). Likewise, at one year, significantly fewer myocardial infarctions occurred with clopidogrel compared to placebo, 4.5% vs. 6.4%, (RR=0.71, 95% CI 0.51-0.99); p=0.038, NNT=55, respectively. No difference between clopidogrel and placebo for urgent revascularization (second PCI or any coronary artery bypass graft procedure on a non-elective basis) was seen at 30 days. The incidence of the composite endpoints of nonfatal MI, urgent target vessel revascularization or CV death at 30 days with clopidogrel compared to placebo was 4.5% and 6.4%, p=0.03, respectively. The incidence of the composite endpoints of cardiovascular death, MI, or any revascularization procedures at 1 year was 18.3% with clopidogrel and 21.7% with placebo, (RR 0.83, 95% CI 0.79-0.99). CREDO trial: The incidence of death from any cause at one year (prespecified secondary analysis) with clopidogrel vs. placebo was not significant. The composite primary endpoint (death, MI, or stroke) was 8.5% with clopidogrel compared with 11.5% with placebo, (RR 0.73, 95% CI 0.57-0.95) at one year The composite endpoint of death, MI or urgent target vessel revascularization at 28 days was not statistically significant. ARMYDA-2 trial: The primary endpoint, composite of death, MI, or target vessel revascularization at 30 days, occurred in 4% of patients receiving 600 mg and 12% of patients receiving 300 mg (p=0.041). The majority of difference in the primary endpoint was due to the increased number of periprocedural MIs that occurred 3 times as often in the clopidogrel 300 mg group compared to the 600 mg group. A 50% risk reduction of MI with the 600 mg loading dose was seen in a multivariable analysis (OR 0.48; 95% CI 0.15 - 0.97; p=0.044). The sample size calculation was based on post-PCI increases in CK-MB levels, and not the primary endpoint.

Key Question 1: Efficacy	Quality of Evidence	Conclusion
Stroke/TIA: comparative efficacy on mortality (all-cause and CV) CV events (MI, stroke) invasive vascular procedure failure (including need for additional invasive vascular procedures)	ERDP/ASA (good) clopidogrel (good) ticlopidine (fair-good)	No head-to-head trials comparing newer antiplatelet agents in stroke/TIA. **ERDP/ASA** (two active-controlled trial) ESPS-2 trial: No difference in all cause mortality (primary endpoint) with ERDP/ASA compared to ERDP vs. ASA vs. placebo was seen. A significant reduction was seen with ERDP/ASA compared to ASA alone for all strokes (p=0.006); non fatal strokes (p=0.004); and combined stroke or TIA (p=0.006) at 24 months. Treatment cessations were 7.2% more frequent in the 2 dipyridamole arms (29.2%) than in the non-dipyridamole arms (22.0%). ESPS-2 was not designed to study the effect of the different treatments on the prevention of MI; when analyzed no statistically significant effect was seen for ASA or extended-release dipyridamole. ESPRIT trial: A lower incidence for the outcome death from all causes and death from all vascular causes with ERDP/ASA compared to ASA was observed. A significant reduction was seen in death from all vascular causes and non-fatal stroke with ERDP/ASA (9.7%) vs. ASA (12.4%) RR 0.78 (95% CI 0.63-0.97). A significant reduction was also seen with ERDP/ASA compared to ASA alone in the first occurrence of the composite death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication: 12.7% vs. 15.7%; RR 0.81, 95% CI 0.67-0.97 (primary endpoint). **Clopidogrel**: (one active-controlled trial) MATCH trial: No difference in death from any cause (secondary endpoint) with clopidogrel plus ASA compared to clopidogrel alone during 18 months of follow-up was observed. No difference was seen either between the two groups for ischemic stroke (fatal or non-fatal); composite ischemic strokes, MI or vascular death. The combination of aspirin plus clopidogrel was no more effective than clopidogrel alone in the composite primary endpoint (ischemic stroke, MI, vascular death, or rehospitalization for acute ischemic events (unstable angina pectoris, worsening of PAD requiring therapeutic intervention, urgent revascularization, or TIA). **Ticlopidine-**(two active-controlled trial) TASS trial: Ticlopidine 250 mg twice a day was slightly more effective than ASA 650 mg twice a day in reducing the risk of death from any cause or nonfatal stroke (primary endpoint) in patients with a history of recent TIA or minor stroke; p=0.048. AAASPS trial: During two year follow-up, no statistical significant difference was observed between ticlopidine and aspirin in the prevention of recurrent stroke, MI, or vascular death in African-American patients with noncardioembolic ischemic stroke.
Predefined group of vascular conditions including PVD: comparative efficacy on all-cause and CV mortality, CV events (stroke, MI) invasive vascular procedure failure (including need for additional invasive vascular procedures	Clopidogrel (good)	There were no head-to-head trials comparing newer antiplatelet agents in PVD. **Clopidogrel:** (one active-controlled trial) The CAPRIE trial had a predefined group of vascular conditions including PVD. A nonsignificant reduction in death from any cause or vascular death was seen with clopidogrel compared to aspirin at 36 months. A significant difference for the combined endpoint of ischemic stroke, MI, or vascular death at 36 months was observed between clopidogrel and aspirin; RR 0.92 (95% CI 0.84-1.00); p=0.043. Clopidogrel did decrease the incidence of AMI at 36 months compared to ASA, p=0.008. The cluster endpoint of amputation, ischemic stroke, MI, or vascular death at 36 months was not significantly different between clopidogrel and aspirin. While a statistical analysis suggested heterogeneity (i.e., an apparent difference in benefit across the three vascular conditions), the reason for the heterogeneity—and the extent to which that might exist—remains unclear. Therefore, subgroup analyses should be interpreted with caution. One such analysis found that PVD patients with marked atherosclerosis had significant benefit with clopidogrel over aspirin in the rate of the primary outcome (3.71% vs. 4.86%; RRR 23.8%, p=0.0028).

Key Question 2: Safety	Quality of Evidence	Conclusion
Adverse effects/events or withdrawals due to adverse effects or serious adverse effects, specific adverse events or withdrawals due to specific adverse events	ERDP/ASA (good) clopidogrel (good) ticlopidine (good)	**ERDP/ASA:** **ESPS-2**: Adverse event rate was high in all the study arms, including with placebo. Headache and diarrhea occurred more frequently and resulted in higher withdrawals rates with ERDP/ASA and ERDP compared to placebo or ASA alone arms. If a patient discontinued therapy due to headache, they usually did it in the first month. At 30 days, GI adverse events accounted for 56.2% treatment cessation in the two ERDP arms and 38% in non-ERDP arms. Severity of the worst bleeding was defined in the following manner: **mild** = requiring no special treatment; **moderate**=requiring specific treatment but no blood transfusion; **severe**= requiring blood transfusion Any of the arms that included ASA had ~2 times more likelihood of bleeding compared to non-ASA arms. **ESPRIT:** Discontinuation of ERDP/ASA occurred in 34% patients due to side-effects, mainly headache (26%). No differences were seen between the ERDP/ASA vs. ASA in the incidence of major or minor bleeding. **Major bleeding:** All intracranial bleeding, any fatal bleeding, or any bleeding requiring hospital admission; 2.6% ERDP/ASA vs. 3.9% ASA HR 0.67, 95% CI 0.44-1.03. **Minor bleeding (not defined in study)**: 12.5% vs. 12.2%; Risk ratio 1.03, 95% CI 0.84-1.25. **Ticlopidine and clopidogrel** have relatively similar adverse effects profile but there are notable differences in the incidence of adverse events. Rash and diarrhea were the most common reasons to stop ticlopidine, more so than with clopidogrel in PCI trials. The incidence of neutropenia associated with clopidogrel has not been noted to the same degree as ticlopidine. ***SUMMARY of Safety Issues per trials involving thienopyridines:*** **CURE: Life threatening bleeding** (fatal or leading to a reduction of Hgb level of at least 5 g/dL, significant hypotension with need of intravenous inotropes, requiring surgical intervention, symptomatic intracranial hemorrhage or requiring blood transfusion of 4 or more units) occurred more frequently with clopidogrel plus aspirin compared to placebo plus ASA but it did not reach statistically significant. **Major bleeding** (disabling bleeding, intraocular bleeding leading to loss of vision or bleeding necessitating blood transfusion of 2 or more units of blood): clopidogrel 3.7% vs. placebo 2.7%, p=0.001 Major bleeding was significantly higher with increasing aspirin doses in both groups. The incidence of bleeding with clopidogrel plus aspirin in doses less than 100 mg/d was less compared to when clopidogrel was used in combination with higher doses of ASA. **Minor bleeding** (defined as other hemorrhages requiring interruption of the drug regimen) was significant with clopidogrel than placebo (5.1% vs. 2.4%, p<0.001). Most common bleeding was GI related: clopidogrel (1.32% vs. 0.7% vs. placebo) and bleeding at arterial puncture sites. The incidence of bleeding decreased over the duration of the study. **CHARISMA: Severe bleeding:** (fatal bleeding and intracranial hemorrhage, or bleeding that caused hemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention was 1.7% in the clopidogrel group and 1.3% in the placebo group, p=0.09. **Moderate bleeding:** (bleeding that led to transfusion but did not meet the criteria for severe bleeding) was significant with clopidogrel than placebo (2.1% vs. 1.3%, p<0.001); **Fatal bleeding** was not significantly different between the treatment groups, (clopidogrel 0.3% vs. placebo 0.2%, p = 0.17). The rate of **intracranial hemorrhage** was similar in the two treatment groups. **CLASSICS**: clopidogrel was better tolerated than ticlopidine. Rash was the frequent reason for discontinuation (2.6% ticlopidine vs. 0.6% clopidogrel). **CREDO:** following PCI, 46% in both clopidogrel and placebo groups permanently discontinued study drug. Of the group that permanently discontinued therapy, 34.5% in the clopidogrel group and 28.3% in the placebo group discontinued study drug due to adverse events. **PCI-CURE:** Types of bleeding are defined similarly as in the CURE trial. No difference in major or minor bleeding at 30 days. At 8 months, minor bleeding was statistically significant in the clopidogrel arm compared to placebo (RR 1.68, 95% CI 1.06-2.69, p = 0.03). **ARMYDA-2**: No significant differences in **minor bleeding** (clinically overt hemorrhage associated with a fall in hemoglobin ≤5 g/dL), entry-site complications, **major bleeding** (intracranial bleeding or clinically overt bleeding associated with a decrease in hemoglobin of >5 g/dL) , thrombocytopenia, or adverse effects requiring clopidogrel discontinuation occurred. Although the safety (secondary) endpoints were similar in the two arms, the study was powered for postprocedural increase of CK-MB levels, instead of the primary endpoint and probably underpowered to draw definitive conclusions about its safety. **MATCH: Life-threatening bleeding** (fatal bleeding event, decrease of Hgb of ≥ 50 g/L, significant hypotension with need for inotropes, symptomatic intracranial hemorrhage or transfusion of ≥ 4 units of RBC in equivalent amount of whole blood): clopidogrel + ASA 2.6% vs. clopidogrel 1.3%, p<0.0001. **Major bleeding** (significantly disabling [with persistent sequelae] intraocular bleeding leading to significant loss of vision, or transfusion of ≤ 3 units RBC or equivalent amount of whole blood): clopidogrel plus ASA 1.9%% vs. 0.6% clopidogrel, p<0.0001. **Minor bleeding:** (reported as an adverse event or serious adverse event by the investigator, according to his clinical judgment): clopidogrel plus ASA 3.2% vs.1% clopidogrel, p<0.0001. **TASS:** Bleeding events including minor symptoms (easy bruising, petechiae, epistaxis and microscopic hematuria) and serious hemorrhages, such as GI bleeding were reported. Nine percent of the patients taking ticlopidine and 10% of those treated with aspirin reported some evidence of bleeding during the trial although about half of the events were thought to be unrelated to the study medication. The events most frequently reported were purpura and epistaxis. Diarrhea occurred in 20% of the patients taking ticlopidine and 10% of those taking aspirin, which led to the discontinuation in 6% and 2% in patients taking ticlopidine and aspirin, respectively. Rash developed in 12% of the patients taking ticlopidine and 5% of those taking aspirin. Discontinuation due to rash was seen in 3% in the ticlopidine group versus 1% in the aspirin group. Severe, but reversible neutropenia occurred in 13 patients assigned to ticlopidine and in none in the aspirin group. Mild-to-moderate neutropenia occurred in 22 patients in the ticlopidine group and in 12 in the aspirin group. **CAPRIE:** The most common reason for adverse event–related early permanent discontinuations was a GI event: 3.21% for clopidogrel and 4.02% for aspirin. Early permanent discontinuations rates for skin and appendage disorders (primarily rash) were more frequent with clopidogrel than with aspirin (1.52% vs. 0.76%). Major/minor bleeding rates were not reported or defined. The frequency of any patient-reported bleeding disorder did not differ significantly between the clopidogrel and the aspirin groups. Intracranial hemorrhage was deemed “severe” by the Central Validation Committee in 30 (0.31%) vs. 40 (0.42%) cases, in the clopidogrel arm vs. aspirin arm. respectively There was a significantly lower incidence of GI bleeding (patient reported) with clopidogrel than with aspirin, (p<0.05). Severe cases, as judged by the investigator occurred in 0.49% with clopidogrel compared to 0.71% of the aspirin cases, p<0.05.

Key Question 3: Subgroups	Quality of Evidence	Conclusion
Age	Inadequate evidence	There are no head-to-head trials or active controlled trials that specifically compare the safety or effectiveness of newer antiplatelet agents by age. In ESPS-2 trial, 42% of the study populations were women. No difference in efficacy or tolerability was noted with age. Inadequate data is available to determine whether one newer antiplatelet agent is superior for a particular age group.
Gender	Inadequate evidence	There are no head-to-head trial or active controlled trials that specifically compare the safety or effectiveness of newer antiplatelet agents by gender Inadequate data is available to determine whether one newer antiplatelet agent is superior based on gender.
Race	ticlopidine (fair/good)	There are no head-to-head trials or active controlled trials that specifically compare the safety or effectiveness of newer antiplatelet agents in patients of a particular race. One study with 100% African American stroke patients evaluated ticlopidine alone to aspirin alone and reported a similar benefit in each group and a similar frequency of adverse effects compared to other studies. Inadequate data is available to determine whether there is a difference between the newer antiplatelet agents for a particular race.
Comorbidities	clopidogrel: subgroup analyses: fair ERDP/ASA: subgroup analyses: fair	Several subgroups of patients have had a favorable response, including diabetics; those with pre-existing atherosclerotic disease, especially symptomatic PAD; and those with a history of previous cardiac surgery. Patients with co-morbidities including history of IHD, IDDM, and NIDDM have also been studied with ERDP/ASA; all subgroups experienced similar stroke prevention benefits. Inadequate data is available to determine whether there is a difference between the newer antiplatelet agents in patients with other comorbidities.
Other medications	clopidogrel: subgroup analyses: (fair) ERDP/ASA: subgroup analyses: (fair)	There are no head-to-head trials or active-controlled trials designed to compare the safety or effectiveness of the newer antiplatelet agents when given concurrently with other medications. Patients enrolled in trials of the newer antiplatelet agents were on a variety of medications including ACE inhibitors, coronary vasodilators, diuretics, peripheral vasodilators, lipid-lowering agents, beta-blockers, calcium channel blockers, GPIIb/IIIa, and anti-diabetic agents. There was no evidence that concurrent use of these drugs leads to differential adverse consequences. However, all the newer antiplatelet agents should be used cautiously with medications that increase the risk for bleeding. Inadequate data is available to determine whether there is a difference between the newer antiplatelet agents administered with other medications.

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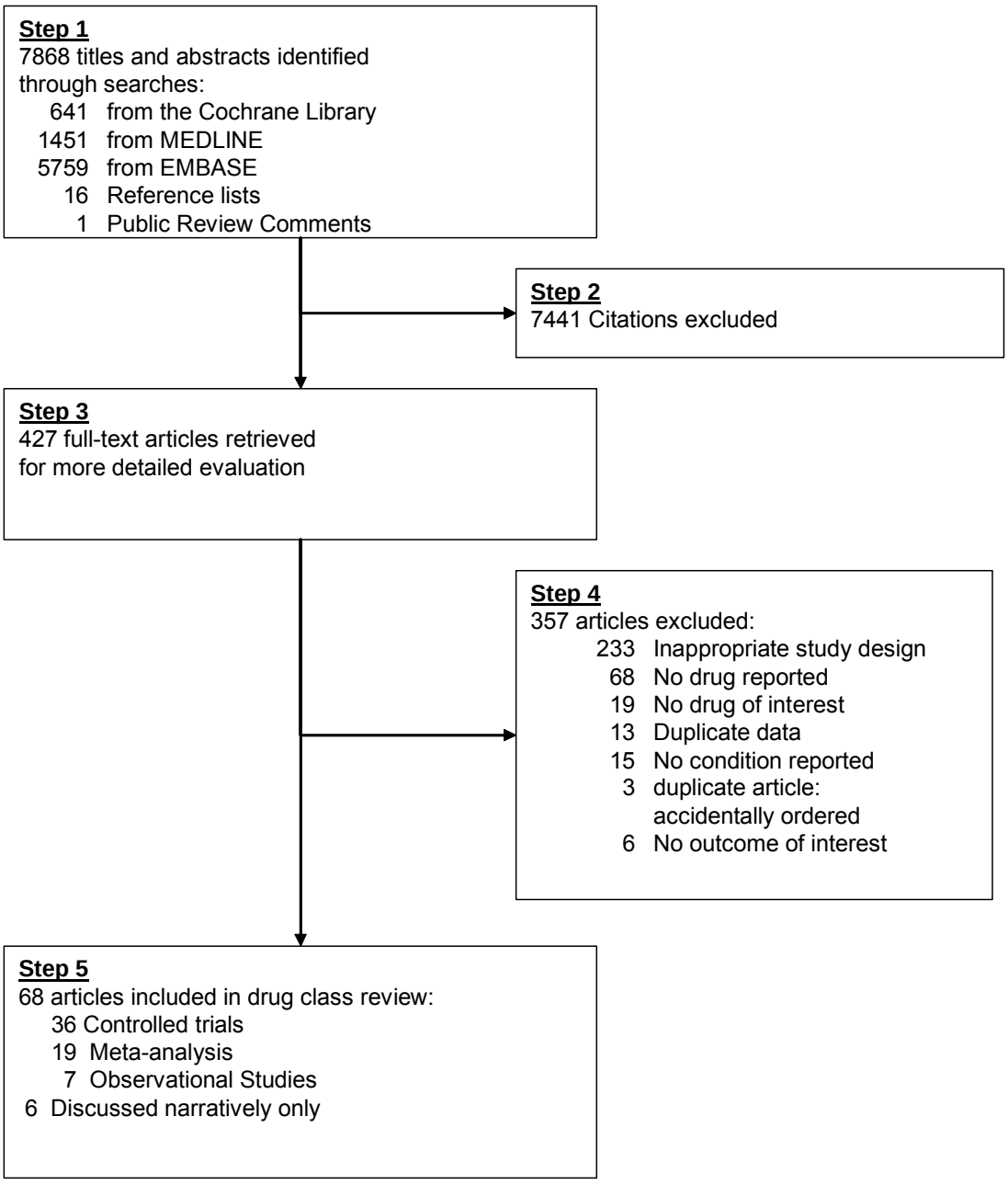
Figure 1. Results of Literature Search



Appendix A. Description and Grade of Recommendations for Level of Evidence

American College of Cardiology and American Heart Association (ACC/AHA): Description of Class 1 with Level of Evidence

Class	**Methodologic Strength of Supporting Evidence**
1	Evidence and/or general agreement that a given procedure or treatment is useful and effective
Level of evidence	
A	Data were derived from multiple large randomized clinical trials
B	Data were derived from limited number of small trials or from nonrandomized studies or observational registries
C	Data were derived from expert opinion, case studies or standard-of-care

American College of Chest Physicians (ACCP): Grade of Recommendations and Strength of Supporting Evidence

Grade of Recommendation	**Clarity of Risk/ Benefit**	**Methodologic Strength of Supporting Evidence**
1A	Clear	Randomized trials without important limitations
1B	Clear	Randomized trials with important limitations (inconsistent results, methodologic flaws)
1C+	Clear	No RCTs, but RCT results can be unequivocally extrapolated, or overwhelming evidence from observation studies
1C	Clear	Observation studies
2A	Unclear	Randomized trials without important limitations
2B	Unclear	Randomized trials with important limitations (inconsistent results, methodology flaws)
2C	Unclear	Observation studies

Appendix B. Search Strategies

ANTIPLATELET THERAPY FOR CORONARY DISEASE, STROKE, AND PERIPHERAL VASCULAR DISEASE –

DATABASES SEARCHED:
PubMed
Embase
Cochrane

TIME PERIOD COVERED: 1994-2004

OTHER LIMITERS:
English
Human

SEARCH STRATEGIES:

SEARCH #1 (PUBMED – Coronary Diseases):
clopidogrel OR Plavix OR ticlopidine OR Ticlid OR (dipyridamole AND aspirin) OR Aggrenox

AND

((coronary disease OR myocardial infarction) AND acute) OR acute coronary syndrome*

AND

clinical trials OR clinical trial[pt] OR controlled clinical trial[pt] OR randomized controlled trial[pt] OR systematic[sb] OR review[pt]

NUMBER OF ITEMS RETRIEVED: 195

SEARCH #2 (PUBMED – Coronary Procedures):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND

coronary artery bypass OR coronary bypass OR angioplasty OR stents[mh] OR stent*[tiab]

AND

clinical trials OR clinical trial[pt] OR controlled clinical trial[pt] OR randomized controlled trial[pt] OR systematic[sb] OR review[pt]

NUMBER OF ITEMS RETRIEVED: 220

SEARCH #3 (PUBMED – Stroke, TIA):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND

cerebrovascular accident OR stroke[tiab] OR ischemic attack, transient OR transient ischemic attack*

AND

clinical trials OR clinical trial[pt] OR controlled clinical trial[pt] OR randomized controlled trial[pt] OR systematic[sb] OR review[pt]

NUMBER OF ITEMS RETRIEVED: 183

SEARCH #4 (PUBMED – Stroke, TIA – Without Trials, Systematic Reviews, Etc.):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND

cerebrovascular accident OR stroke[tiab] OR ischemic attack, transient OR transient ischemic attack*

NUMBER OF ITEMS RETRIEVED: 380

SEARCH #5 (PUBMED – Coronary Diseases – Excluding Trials, Systematic Reviews, Etc.):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND

((coronary disease OR myocardial infarction) AND acute) OR acute coronary syndrome*

NOT

clinical trials OR clinical trial[pt] OR controlled clinical trial[pt] OR randomized controlled trial[pt] or systematic OR review[pt]

NUMBER OF ITEMS RETRIEVED: 79

SEARCH #6 (PUBMED – Peripheral Vascular Disease):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND

peripheral vascular diseases OR peripheral vascular disease*[tiab]

NUMBER OF ITEMS RETRIEVED: 58

SEARCH #7 (Embase – Coronary Diseases & Procedure – Clinical Trials):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND (acetylsalicylic acid OR aspirin))

AND

coronary artery disease[Exploded] OR ischemic heart disease[Exploded] OR coronary artery bypass OR angioplasty/TI,DE OR stent*/TI,DE

AND

outcome* OR effective* OR efficac* OR mortality OR adverse OR safe*

AND

clinical trial* OR controlled trial*

NUMBER OF ITEMS RETRIEVED: 1571

SEARCH #8 (Embase – Coronary Diseases & Procedures – Systematic Reviews):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND (acetylsalicylic acid OR aspirin))

AND

coronary artery disease[Exploded] OR ischemic heart disease[Exploded] OR coronary artery bypass OR angioplasty/TI,DE OR stent*/TI,DE

AND

outcome* OR effective* OR efficac* OR mortality

AND

systematic review*

NUMBER OF ITEMS RETRIEVED: 17

SEARCH #9 (Embase – Coronary Diseases & Procedures – Safety/Adverse effects)):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND (acetylsalicylic acid OR aspirin))

AND

coronary artery disease[Exploded] OR ischemic heart disease[Exploded] OR coronary artery bypass OR angioplasty/TI,DE OR stent*/TI,DE

AND

adverse or safe*

NOT

Results of Searches #7 OR #8

NUMBER OF ITEMS RETRIEVED: 644

SEARCH #10 (Embase – Ticlopidine (NICE search strategy)):

ticlopidine

AND

heart infarction! OR myocard* infarc*/ti OR mi/ti OR nstemi/ti,ab OR non st segment elevation myocardial infarction/ti,ab OR stroke/ti OR cerebrovascular accident OR cerebrovascular accident*/ti OR cva/ti OR transient ischemic attack or (isch*emic stroke OR transient isch*emic attack*)/ti,ab OR unstable angina pectoris OR unstable angina/ti,ab OR peripheral, arterial disease/ti,ab OR tia/ti OR tias/ti

AND

randomi* controlled trial*/ti,ab OR randomization OR random allocation/ti,ab,OR (double OR single) blind procedure OR clin*(2w)trial*/ti,ab OR random/ti,ab OR methodology/de OR (sing* OR doubl* OR trebl* OR tripl*)(2w)(method OR blind*OR mask?)/ti,ab OR placebo/de OR placebo*/ti,ab OR research design/ti,ab OR comparative study OR follow up OR evaluation/de OR (control OR controls OR controlled)/ti,ab OR phase 4 clinical trial OR phase 4/ti,ab OR phase four/ti,ab OR phase iv/ti,ab OR postmarketing surveillance OR post market*surveillance/ti,ab

NUMBER OF ITEMS RETRIEVED: 713

SEARCH #11 (Cochrane - Coronary Diseases & Procedures):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND

((coronary disease* or myocardial infarction) and acute) OR acute coronary syndrome* or coronary artery bypass) OR coronary bypass OR angioplasty OR stent OR stents

NUMBER OF ITEMS RETRIEVED: 261

SEARCH #12 (Cochrane – Stroke, TIA):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND

cerebrovascular accident or stroke or transient ischemic attack

NUMBER OF ITEMS RETRIEVED: 170

SEARCH #13 (Cochrane – Peripheral Vascular Disease):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND

peripheral vascular disease

NUMBER OF ITEMS RETRIEVED: 4

Search Strategy for Report Update

DATABASE SEARCHED:
PubMed
Cochrane – Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Central Register of Controlled Trials
Embase

TIME PERIOD COVERED: 2004-5/19/2006

OTHER LIMITERS:
English
Human

SEARCH STRATEGIES:

SEARCH #1A (PUBMED – Coronary Diseases + Clinical Trials):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND

((coronary disease OR myocardial infarction) AND acute) OR acute coronary syndrome*

AND

clinical trials OR clinical trial[pt] OR controlled clinical trial[pt] OR randomized controlled trial[pt] OR systematic[sb] OR review[pt]

NUMBER OF ITEMS RETRIEVED: 83

SEARCH #1B (PUBMED – Coronary Diseases NOT Clinical Trials):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND

((coronary disease OR myocardial infarction) AND acute) OR acute coronary syndrome*

NOT

clinical trials OR clinical trial[pt] OR controlled clinical trial[pt] OR randomized controlled trial[pt] OR systematic[sb] OR review[pt]

NUMBER OF ITEMS RETRIEVED: 42

SEARCH #2 (PUBMED – Coronary Procedures):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND

(coronary artery bypass OR coronary bypass OR angioplasty OR stents[mh] OR stent*[tiab])

AND

clinical trials OR clinical trial[pt] OR controlled clinical trial[pt] OR randomized controlled trial[pt] OR systematic[sb] OR review[pt]

NOT

Results of Search #1

NUMBER OF ITEMS RETRIEVED: 101

SEARCH #3A (PUBMED – Stroke/TIA + Clinical Trials):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND
cerebrovascular accident OR stroke[tiab] OR ischemic attack, transient OR transient ischemic attack*)

AND

clinical trials OR clinical trial[pt] OR controlled clinical trial[pt] OR randomized controlled trial[pt] OR systematic[sb] OR review[pt]

NOT

Results of Search #1 OR #2

NUMBER OF ITEMS RETRIEVED: 53

SEARCH #3B (PUBMED – Stroke/TIA NOT Clinical Trials):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND
cerebrovascular accident OR stroke[tiab] OR ischemic attack, transient OR transient ischemic attack*)

NOT

clinical trials OR clinical trial[pt] OR controlled clinical trial[pt] OR randomized controlled trial[pt] OR systematic[sb] OR review[pt]

NOT

Results of Search #1 OR #2

NUMBER OF ITEMS RETRIEVED: 45

SEARCH #4 (PUBMED – Peripheral Vascular Disease):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox

AND
cerebrovascular accident OR stroke[tiab] OR ischemic attack, transient OR transient ischemic attack*)

AND

clinical trials OR clinical trial[pt] OR controlled clinical trial[pt] OR randomized controlled trial[pt] OR systematic[sb] OR review[pt]

AND

peripheral vascular diseases OR peripheral vascular disease*[tiab])

NOT

Results of Search #1 OR #2 OR #3

NUMBER OF ITEMS RETRIEVED: 12

SEARCH #5 (Cochrane - Coronary Diseases & Procedures):

(clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox).mp. NOTE – "mp"=title, abstract, MESH headings, keywords, full text, caption text]

AND

(((coronary disease$ OR myocardial infarction) AND acute) OR acute coronary syndrome$ OR coronary artery bypass OR coronary bypass OR angioplasty OR stent OR stents).mp.

NUMBER OF ITEMS RETRIEVED: 117

SEARCH #6 (Cochrane - Stroke & TIA):

clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox).mp.

AND

(cerebrovascular accident or stroke or transient ischemic attack$).mp

NUMBER OF ITEMS RETRIEVED: 71

SEARCH #7 (Cochrane - Peripheral Vascular Disease):

clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND aspirin) OR aggrenox).mp.

AND

peripheral vascular disease$.mp.
NUMBER OF ITEMS RETRIEVED: 18

SEARCH #8A (Embase - Coronary Diseases & Procedures – Clinical Trials):

clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND (acetylsalicylic acid OR aspirin))

AND

coronary artery disease! OR ischemic heart disease! OR coronary()artery()bypass OR angioplasty/ti,de OR stent?/ti,de

AND

outcome? OR effective? OR efficac? OR mortality OR adverse OR safe?

AND

clinical()trial? OR controlled()trial?

NUMBER OF ITEMS RETRIEVED: 1064

SEARCH #8B (Embase - Coronary Diseases & Procedures – Systematic Reviews):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND (acetylsalicylic acid OR aspirin))

AND

coronary artery disease! OR ischemic heart disease! OR coronary()artery()bypass OR angioplasty/ti,de OR stent?/ti,de

AND

outcome? OR effective? OR efficac? OR mortality OR adverse OR safe?

AND

systematic()review?

NOT

Results of Embase Search #1A

NUMBER OF ITEMS RETRIEVED: 2

SEARCH #8C (Embase - Coronary Diseases & Procedures –Adverse Effects & Safety):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND (acetylsalicylic acid OR aspirin))

AND

coronary artery disease! OR ischemic heart disease! OR coronary()artery()bypass OR angioplasty/ti,de OR stent?/ti,de

AND

adverse? OR safe?

NOT

Results of Embase Searches #1A & 1B

NUMBER OF ITEMS RETRIEVED: 406

SEARCH #9 (Embase - Stroke/TIA):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND (acetylsalicylic acid OR aspirin))

AND

stroke/ti,de OR cerebrovascular disease! OR transient()ischemic()attack?)

NOT

Results of previous Embase searches

NUMBER OF ITEMS RETRIEVED: 589

SEARCH #10 (Embase - PVD):
clopidogrel OR plavix OR ticlopidine OR ticlid OR (dipyridamole AND (acetylsalicylic acid OR aspirin))

AND

peripheral vascular disease! OR peripheral()vascular()disease?

NOT

Results of previous Embase searches

NUMBER OF ITEMS RETRIEVED: 711

SEARCH #11 (Embase - "NICE" Search Strategy - TICLOPIDINE):
ticlopidine

AND

heart infarction! OR myocard?()infarc?/ti OR mi/ti OR nstemi/ti,ab OR non()st()segment()elevation()myocardial()infarction/ti,ab OR stroke/ti OR cerebrovascular accident OR cerebrovascular()accident?/ti OR cva/ti OR transient ischemic attack OR isch?emic()stroke OR transient()isch?emic()attack?/ti,ab OR unstable angina pectoris OR unstable()angina/ti,ab OR peripheral()arterial()disease/ti,ab OR tia/ti OR tias/ti

AND

randomi?()controlled()trial?/ti,ab or randomization OR random()allocation/ti,ab OR (double OR single)()blind()procedure OR clin?(2w)trial?/ti,ab OR random/ti,ab OR methodology/de OR (sing? OR

doubl? OR trebl? OR tripl?)(2w)(method OR blind? OR mask?)/ti,ab OR placebo/de OR placebo?/ti,ab OR research()design/ti,ab OR comparative study OR follow up OR evaluation/de OR control OR controls OR controlled)/ti,ab OR phase 4 clinical trial OR phase()4/ti,ab OR phase()four/ti,ab OR phase()iv/ti,ab OR postmarketing surveillance OR post()market?()surveillance/ti,ab

NOT

Results of previous Embase searches

NUMBER OF ITEMS RETRIEVED: 42

Appendix C. Quality assessment methods for drug class reviews for DERP

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are 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 *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
Adequate approaches to sequence generation:
Computer-generated random numbers
Random numbers tables
Inferior approaches to sequence generation:
Use of alternation, case record numbers, birth dates or week days
Not reported

2. Was the treatment allocation concealed?
Adequate approaches to concealment of randomization:
Centralized or pharmacy-controlled randomization
Serially-numbered identical containers
On-site computer based system with a randomization sequence that is not readable until allocation
Other approaches sequence to clinicians and patients

Inferior approaches to concealment of randomization:
Use of alternation, case record numbers, birth dates or week days
Open random numbers lists
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of

study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that

studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix D. Bibliography of Excluded Articles

1. Erratum: Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death , myocardial infarction, and stroke in high risk patients (BMJ (12 January) (71)). BMJ 2002;324(7330):141.

2. Albers GW, Amarenco P. Combination therapy with clopidogrel and aspirin: can the CURE results be extrapolated to cerebrovascular patients? Stroke 2001;32(12):2948-9.

3. Albiero R, Hall P, Itoh A, et al. Results of a consecutive series of patients receiving only antiplatelet therapy after optimized stent implantation. Comparison of aspirin alone versus combined ticlopidine and aspirin therapy. Circulation 1997;95(5):1145-56.

4. Algra A, van GJ. Is clopidogrel superior to aspirin in secondary prevention of vascular disease? CCTCM. 2000;1(3):143-145.

5. Angioi M, Danchin N, Alla F, et al. Long - term outcome in patients treated by intracoronary stenting with ticlopidine and aspirin, and deleterious prognostic role of unstable angina pectoris. Am J Cardio. 2000;85(9):1065-1070.

6. Ashby DT, Dangas G, Mehran R, et al. Comparison of one-year outcomes after percutaneous coronary intervention among current smokers , ex-smokers, and nonsmokers. Am J Cardiol 2002;89(2):221-224.

7. Ashby DT, Mehran R, Aymong EA, et al. Comparison of outcomes in men versus women having percutaneous coronary interventions in small coronary arteries. Am J Cardiol 2003;91(8):979-981.

8. Baigent C, Sudlow C, Collins R, et al. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death , myocardial infarction, and stroke in high risk patients. BMJ 2002;324(7329):71-86.

9. Becquemin JP. Effect of ticlopidine on the long-term patency of saphenous-vein bypass grafts in the legs. Etude de la Ticlopidine apres Pontage Femoro-Poplite and the Association Universitaire de Recherche en Chirurgie. N Engl J Med 1997;337(24):1726-31.

10. Bednar MM, Gross CE. Antiplatelet therapy in acute cerebral ischemia. Stroke 1999;30(4):887-93.

11. Bennett CL, Connors JM, Carwile JM, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. N Engl J Med 2000;342(24):1773-7.

12. Bennett CL, Davidson CJ, Raisch DW, et al. Thrombotic thrombocytopenic purpura associated with ticlopidine in the setting of coronary artery stents and stroke prevention. Arch Intern Med 1999;159(21):2524-8.

13. Bennett CL, Weinberg PD, Rozenberg-Ben-Dror K, et al. Thrombotic thrombocytopenic purpura associated with ticlopidine. A review of 60 cases. Ann Intern Med 1998;128(7):541-4.

14. Berger PB, Bell MR, Grill DE, et al. Frequency of adverse clinical events in the 12 months following successful intracoronary stent placement in patients treated with aspirin and ticlopidine (without warfarin). Am J Cardiol 1998;81(6):713-718.

15. Berger PB, Bell MR, Hasdai D, et al. Safety and efficacy of ticlopidine for only 2 weeks after successful intracoronary stent placement. Circulation 1999;99(2):248-53.

16. Berger PB, Bell MR, Rihal CS, et al. Clopidogrel versus ticlopidine after intracoronary stent placement. J Am Coll Cardiol 1999;34(7):1891-4.

17. Berger PB, Mahaffey KW, Meier SJ, et al. Safety and efficacy of only 2 weeks of ticlopidine therapy in patients at increased risk of coronary stent thrombosis: results from the Antiplatelet Therapy alone versus Lovenox plus Antiplatelet therapy in patients at increased risk of Stent Thrombosis (ATLAST) trial. Am Heart J 2002;143(5):841-6.

18. Berger PB, Vladimir D, Penn IM, et al. Does ticlopidine reduce reocclusion and other adverse events after successful balloon angioplasty of occluded coronary arteries? Results from the total occlusion study of Canada (TOSCA). Am Heart J 2001;142(5):776-781.

19. Berglund U, Lindahl T. Enhanced onset of platelet inhibition with a loading dose of ticlopidine in ASA-treated stable coronary patients. Int J Cardiol 1998;64(2):215-7.

20. Bertrand ME, Legrand V, Boland J, et al. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation versus aspirin and ticlopidine (fantastic) study. Circulation 1998;98 (16):1597-603.

21. Bertrand ME, Rupprecht HJ, Urban P, et al. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation 2000;102(6):624-9.

22. Bhatt DL, Chew DP, Hirsch AT, et al. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. Circulation 2001;103(3):363-8.

23. Bhatt DL, Hirsch AT, Ringleb PA, et al. Reduction in the need for hospitalization for recurrent ischemic events and bleeding with clopidogrel instead of aspirin. CAPRIE investigators. Am Heart J 2000;140(1):67-73.

24. Bhatt DL, Marso SP, Hirsch AT, et al. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. Am J Cardiol 2002;90(6):625-8.

25. Blecic S. Atherothrombotic events often indicate disseminated atherosclerosis: data from CAPRIE. Cerebrovas Dis 1998;8:34.

26. Boysen G. Bleeding complications in secondary stroke prevention by antiplatelet therapy: a benefit-risk analysis. J Intern Med 1999;246(3):239-45.

27. Budaj A, Yusuf S, Mehta SR, et al. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. Circulation 2002;106(13):1622-6.

28. Cannon CP. Effectiveness of clopidogrel versus aspirin in preventing acute myocardial infarction in patients with symptomatic atherothrombosis (CAPRIE trial). Am J Cardiol 2002;90(7):760-2.

29. Caro JJ, Migliaccio-Walle K. Generalizing the results of clinical trials to actual practice: the example of clopidogrel therapy for the prevention of vascular events. CAPRA (CAPRIE Actual Practice Rates Analysis) Study Group. Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events. Am J Med 1999;107(6):568-72.

30. Chan AW, Moliterno DJ, Berger PB, et al. Triple antiplatelet therapy during percutaneous coronary intervention is associated with improved outcomes including one-year survival: results from the Do Tirofiban and ReoProGive Similar Efficacy Outcome Trial (TARGET). J Am Coll Cardiol 2003;42(7):1188-95.

31. Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus Aspirin and Esomeprazole to Prevent Recurrent Ulcer Bleeding. N Engl J Med 2005;352(3):238-244.

32. Cin VG, Temizhan A, Pekdemir H, et al. The effects of ticlopidine in acute myocardial infarction as an adjunctive treatment to aspirin in an intermediate term setting. Turkish Journal of Medical Sciences 2002;32(4):329-334.

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Appendix E. Drug Interactions with the Newer Antiplatelet Agents

Clopidogrel

NSAIDs	In healthy volunteers receiving naproxen, clopidogrel was associated with increased occult GI blood loss. NSAIDS and clopidogrel should be administered with caution
Warfarin	Concomitant administration with clopidogrel should be with caution due to the increase risk of bleeding

ERDP/ASA

Adenosine	Dipyridamole has been reported to increase the plasma levels and CV effects of adenosine
ACE Inhibitors	Hyponatremic and hypotensive effects of ACE inhibitors may be diminished with ASA concomitant
Acetazolamide	Leads to high serum concentration with concurrent use of aspirin
Heparin/warfarin	Prolongation of protime/INR with ASA
Anticonvulsants	Displace phenytoin and valproic acid with ASA
Beta Blockers:	Hypotensive effects can be diminished by the concomitant administration of ASA
Cholinesterase Inhibitors:	Anticholinesterase effect of agents may be diminished with dipyridamole
Diuretics:	Effectiveness of agents may be diminished with concomitant administration of ASA
Methotrexate	Inhibit renal clearance of agent by ASA
NSAID	Potentially increase bleeding and decreased renal function
Oral hypoglycemic	Effectiveness of agents may increase with moderate doses of aspirin

Ticlopidine

Antacids	Giving ticlopidine after antacids has resulted in 18% decrease in ticlopidine plasma level
Cimetidine	Chronic cimetidine has reduced the clearance of single ticlopidine dose by 50%
Digoxin	Coadministration of ticlopidine with digoxin resulted in a slight decrease (approximately 15%) in digoxin plasma levels. Little or no change in therapeutic efficacy of digoxin would be expected.
Propranolol	In vitro studies demonstrated that ticlopidine does not alter the plasma protein binding of propranolol. However, the protein binding interactions of ticlopidine and its metabolites have not been studied in vivo. Caution should be exercised in coadministering propranolol with ticlopidine.
Phenytoin	In vitro studies, ticlopidine does not alter the plasma protein binding of phenytoin. However, the protein binding interactions of ticlopidine and is metabolites have not been studied in vivo. Several cases of elevated phenytoin plasma levels with associated somnolence and lethargy have been reported following coadministration with ticlopidine. Caution should be exercised in coadministering this drug with ticlopidine, and it may be useful to remeasure phenytoin blood concentrations
Theophylline	Concomitant administration of ticlopidine resulted in a significant increase in the theophylline elimination half-life from 8.6 to 12.2 hours and a comparable reduction in total plasma clearance of theophylline

Appendix F: Definitions of the FDA Pregnancy Categories

FDA pregnancy category	Definition
A	Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
B	No evidence of risk in humans. Either animal findings show risk, but human findings do not; or if no adequate human studies have been done, animal findings are negative.
C	Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking. However, potential benefits may justify the potential risks.
D	Positive evidence of risk. Investigational or post-marketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risks. If needed in a life-threatening situation or a serious disease, the drug may be acceptable if safer drugs cannon be used or are ineffective.
X	Contraindicated in pregnancy. Studies in animals or human, or investigational or post-marketing reports have shown fetal risk which clearly outweighs any possible benefit to the patient.