Drug Class Review
on
Newer Antiplatelet Agents

Final Report

November 2005

The Agency for Healthcare Research and Quality has not yet seen or approved this report

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.

Janet H. Dailey, PharmD
Peter Glassman, MBBS, MSc
Marika Suttorp, MS
Cony Rolón, BA

Produced by
Southern California Evidence-based Practice Center
RAND
1700 Main Street, PO Box 2138
Santa Monica, CA 90407

Paul Shekelle, co-Director
Sally Morton, co-Director

Copyright © 2005 by Oregon Health & Science University
Portland, Oregon 97201. All rights reserved.

TABLE OF CONTENTS

INTRODUCTION

I. Scope of the problem

Atherosclerosis often starts in late adolescence or early adulthood, although clinical manifestations typically occur years later. Statistics from 2002 indicate that approximately 70.1 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 2,600 Americans die of CVD each day, an average of 1 death every 34 seconds. Over 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. Peripheral arterial disease frequently manifests as intermittent claudication of the lower extremity, though other presentations include arterial aneurysms, typically of the aorta, and renovascular disease.

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. 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) 25mg /extended-release dipyridamole 200mg (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.

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[2] (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. Aspirin should be administered as soon as possible after presentation and continued indefinitely (Level of Evidence: A).
2. Clopidogrel should be administered to hospitalized patients who are unable to take ASA because of hypersensitivity or major GI intolerance (Level of Evidence: A).
3. 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).

4. 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).
5. 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[3] 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] recommends the following: (Appendix A describes the ACCP method of grading evidence.)

1. For ACS, aspirin should be given at initial doses of 160mg to 325mg and then indefinitely at 75 to162mg daily (Grade 1A).
2. 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).
3. For all NSTE ACS patients with an aspirin allergy, immediate treatment with clopidogrel, 300mg bolus oral, followed by 75mg/d indefinitely (Grade 1A).
4. A combination of aspirin and ticlopidine or aspirin and clopidogrel is preferred over systemic anticoagulation therapy following stent placement (Grade 1A).
5. Clopidogrel is preferred over ticlopidine following stent placement. (Grade 1A)
6. A loading dose of 300mg 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 600mg loading dose of clopidogrel is suggested (Grade 2C).
7. For PCI patients who cannot tolerate aspirin, clopidogrel 300mg or ticlopidine 500mg may be administered at least 24 hours prior to planned PCI (Grade 2C).
8. 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 (300mg), followed by 75mg/d for 9-12 months in addition to aspirin (Grade 1A).
9. For chronic limb ischemia, clopidogrel rather than ticlopidine should be used (Grade 1C+); aspirin should be used instead of clopidogrel (Grade 2A).
10. 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).

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

Table 1. FDA Approved Indications* and Use of Selected Antiplatelet Agents in Acute Coronary Syndrome, Stroke/TIA, and Peripheral Vascular Disease

Agents	Date Approved	FDA Approved Indications	ACS	Post-Stent	Stroke/ TIA	PVD
ASA /extended-release dipyridamole 25mg/200mg (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 a thrombotic event 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)	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; ACS= acute coronary syndrome; TIA= transient ischemic attack; PVD= peripheral vascular disease.

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 intervention procedures, prior ischemic stroke or TIA, or symptomatic peripheral vascular disease do antiplatelets differ in effectiveness?
2. For adults with acute coronary syndromes or coronary intervention procedures, 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

Populations

Adult patients with

- Acute coronary syndrome
- Coronary intervention procedures (angioplasty, stents and bypass surgery)
- Prior ischemic stroke or TIA
- Symptomatic peripheral vascular disease

Interventions

- Clopidogrel (as monotherapy or in combination with aspirin)
- Ticlopidine (as monotherapy or in combination with aspirin)
- Extended-Release dipyridamole and aspirin

Outcomes

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

Table 2. Eligible Outcomes

Populations	Outcome for all populations
Acute coronary syndrome	1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, MI) 3. Invasive vascular procedure failure (including need for additional invasive vascular procedures

Populations	Outcome for all populations
Coronary intervention procedures (angioplasty, stents and bypass surgery)	1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, MI 3. Invasive vascular procedure failure (including need for additional invasive vascular procedures
Prior ischemic stroke or TIA	1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, MI) 3. Invasive vascular procedure failure (including need for additional invasive vascular procedures
Symptomatic peripheral vascular disease	1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, MI) 3. Invasive vascular procedure failure (including need for additional invasive vascular procedures

Safety Outcomes

- Serious adverse events reported
- Overall adverse effects reported
- Withdrawals due to adverse effects
- 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, systematic reviews
- For safety: in addition to head-to-head and controlled clinical trials, 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 Sept. /Oct. 2004), Embase (1994 to Nov. 2004), the Cochrane Central Register of Controlled Trials (Fall 2004), 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[5] and Clopidogrel[6] dossiers were received) including citations. 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. 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 had compared an antiplatelet agent to placebo, because the acceptable standard of care today would more than likely (if clinically warranted and possible) include at least ASA therapy. Lastly, only trials that specifically utilized Aggrenox® 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).

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 likely to occur in patients with peripheral vascular disease as they are in patients with prior ischemic stroke or even normals. 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.[7]

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 4512 total citations: 435 from the Cochrane Library, 1115 from MEDLINE, and 2945 from EMBASE. Additional review identified 16 citations from reference lists. An additional article was suggested after public review. One hundred and sixty articles were considered relevant to the topic and screened. One hundred and twenty-one articles were rejected; study design not appropriate (51); no drug reported (27); no drug of interest (19);

duplicate data (13); no condition reported (3); duplicate article accidentally ordered (3); no outcome of interest (5).

Thirty-nine articles were included in the drug class review; 19 randomized controlled trials, 3 observational studies; 11 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 19 controlled trials and three 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: Large clinical trials included per types of study population

Trial name	Interventions	Description of trial
Acute Coronary Syndrome (ACS)		
CURE[8]	C 300mg x 1 (loading dose) or matching placebo; then C 75mg vs. placebo with ASA (75-325mg) daily in both arms	Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) randomly assigned 12,562 ACS patients to receive clopidogrel 300mg immediately, followed by 75mg once daily or placebo in addition to aspirin for 3–12 months.
Percutaneous Coronary Interventions (PCI)		
CLASSICS[9]	C 300mg X1 (loading dose) + 325mg ASA on day 1; then C 75mg plus ASA 325mg daily vs. C 75mg plus ASA 325mg daily vs. T 250mg twice a day plus ASA 325mg daily	The Clopidogrel Aspirin stent International Cooperative Study (CLASSICS) evaluated the safety of clopidogrel (with or without a loading dose) in combination with aspirin compared with ticlopidine in combination with aspirin in patients who had undergone successful coronary stent procedure. Patients were followed for 28 days.
PCI-CURE[10]	After PCI, open-label C or T plus ASA (75-325mg) x 2-4 weeks then assigned study medication resumed (per CURE trial) with ASA (75-325mg) daily in both arms	Prospectively designed study involving 2658 patients undergoing PCI who were randomized to a double-blind therapy with clopidogrel or placebo in the CURE trial. Patients were followed for up to 1 year.
CREDO[11]	C 300mg X1 (loading dose) or matching placebo plus ASA 325mg. Post-PCI: C 75mg plus ASA 325mg x 28 days; then C 75mg daily vs. placebo from day 29 through 12 months with ASA (81-325mg) daily in both arms	Clopidogrel for the Reduction of Events During Observation (CREDO) evaluated the efficacy and safety of clopidogrel therapy for 1 year and the efficacy and safety of a loading dose of clopidogrel prior to elective PCI in 2116 patients.
Stroke		
ESPS-2[12]	ASA 25mg twice a day vs. ERDP 200mg twice a day vs. ERDP 200mg /ASA 25mg twice a day vs. placebo twice a day	The European Stroke Prevention Study 2 (ESPS-2) investigated the safety and efficacy of low-dose ASA, extended- release dipyridamole, and the two agents in combination for secondary prevention of ischemic stroke. Patients were followed for 2 years.
MATCH[13]	C 75mg plus ASA 75mg daily vs. C 75mg plus ASA placebo daily	The Management of Atherothrombosis with Clopidogrel in High-Risk Patients evaluated the risk of recurrent ischemic vascular events (MATCH) with clopidogrel 75mg vs. clopidogrel 75mg and aspirin 75mg in 7599 patients with a follow-up of 81 months. The high-risk patients had a history of a previous ischemic stroke or TIA within 3 months of randomization and at least one additional vascular risk factor within the preceding three years and who were already receiving clopidogrel 75mg/d. The duration of treatment and follow-up was 18 months.
TASS[14]	T 250mg twice a day vs. ASA 650mg twice a day	Ticlopidine Aspirin Stroke Study (TASS) compared the effects of ticlopidine with those of aspirin on the risk of stroke or death in 3069 patients with recent transient or mild persistent focal cerebral or retinal ischemia. Patients were followed for 2-6 years.
Predefined Group of Vascular Conditions Including Peripheral Vascular Disease		
CAPRIE[15]	C 75mg + ASA placebo vs. ASA 325mg + C placebo daily	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) evaluated the potential benefit of clopidogrel compared to aspirin in reducing the risk of ischemic stroke, myocardial infarction, or vascular death in a subgroup of patients including those with recent ischemic stroke, recent myocardial infarction, or peripheral arterial disease. Patients were followed for 1-3 years.

ASA = aspirin, ERDP = extended-release dipyridamole, C = clopidogrel, T = ticlopidine.

Key Question 1. For adult patients with coronary syndromes or coronary intervention procedures, prior ischemic stroke or TIA, or symptomatic peripheral vascular disease, do antiplatelets differ in effectiveness?

Key Question 1a. In patients with acute coronary syndromes, what is the comparative efficacy of the newer antiplatelet agents in all-cause and cardiovascular mortality, cardiovascular events (stroke, MI), 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 acute coronary syndrome (ACS)

The largest body of evidence exists for clopidogrel in patients with ACS. No data exists for ticlopidine or extended-release dipyridamole in patients with ACS.

Efficacy Trials: (ACS)

- No head-to-head trials of the newer antiplatelet agents in ACS were identified. The medications ticlopidine and ERDP/ASA have not been studied for efficacy and safety in the setting of ACS.

- Active-controlled trial: One good-quality, multicenter randomized controlled trial (RCT) (CURE)[8] was evaluated.
  - The CURE[8] trial compared the efficacy and safety of clopidogrel and aspirin in 12,562 patients with ACS. The patients were randomized to clopidogrel (300mg loading dose, 75mg daily thereafter) plus aspirin or placebo plus aspirin for a mean of 9 months. The average dose of aspirin in both arms was 150mg. Patients enrolled in CURE 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 2b/3a agents, were typically lower than the rates at many U.S. centers. Nevertheless, clopidogrel plus aspirin reduced the rates of CV death, nonfatal MI, and 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 very high rate of temporary (~45%) and permanent (~20%) discontinuation of the study medications.

- Two meta-analyses[16, 17] 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 trial: In the CURE[8] trial, adding clopidogrel to aspirin provided benefit regardless of the aspirin dose but with a higher incidence of bleeding. For patients with ACS, major bleeding occurred in 2.7% of patients in the aspirin alone group and 3.7% in the clopidogrel/aspirin group, yielding a 38% increase in major bleeding complications (p=0.001). Minor bleeding episodes were twice as common with clopidogrel than placebo (5.1% vs. 2.4%; p<0.001). A post-hoc analysis from the CURE trial suggests that lower aspirin doses (75-100mg) have a more favorable safety profiles in terms of bleeding rates compared to when clopidogrel was combined with higher doses of aspirin.
- If aspirin is chosen as the principal antiplatelet agent and upper GI bleeding occurs, a recent randomized controlled study[18] 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 in patients undergoing PCI.

- Eight head-to-head trials were identified, only one[9] of which was judged to be of good quality.
  - The CLASSICS[9] trial was primarily a safety study. The secondary outcomes in that trial were major adverse clinical events (MACE) including MI (fatal and non-fatal), MI plus target lesion revascularization (TLR), and sudden death. The 30-day rate for MACE was similar between ticlopidine and clopidogrel ($p \geq 0.5$).

- Active-controlled trials: Two good-quality, multicenter randomized controlled trials[10, 11] (RCTs) in patients with PCI were evaluated.

- The PCI-CURE[10] 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 and after PCI. PCI-CURE found that with long-term (8 months on average) administration of clopidogrel and aspirin after PCI, rates of CV death, MI, or any revascularization were lower. A statistical significant difference in minor bleeding episodes was seen with clopidogrel plus aspirin arm compared to the placebo plus aspirin arm (RR 1.68, 95% CI 1.06-2.68, p=0.03).
- The CREDO[11] trial demonstrated a long-term (1-year) reduction in CV events in patients undergoing PCI with clopidogrel and aspirin. Pretreatment loading dose of clopidogrel ≥ 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.

- Two meta-analyses[19, 20] which compared clopidogrel and ticlopidine following stent placement procedure were included. The meta-analysis performed by Casella et al.[19] 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.[20] 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:

- Head-to-Head Trial: In the 28 day CLASSICS[9] trial, the primary endpoint consisted of 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. The primary endpoint occurred in 9.1% of patients in the ticlopidine group and 4.6% of patients in the combined clopidogrel groups (RR 0.50, 95% CI 0.31-0.81;p=0.005). Skin disorders, primarily rash, were the most frequent reason for discontinuing therapy, with incidences of 2.6% in ticlopidine users and 0.6% in clopidogrel users. 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 have relatively similar adverse effects profile but there are notable differences. 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 ticlopidine has not been noted to the same degree with clopidogrel.

- Based on adverse event profiles, clopidogrel alone is safer than ticlopidine, and is as safe as aspirin. Thienopyridines were associated with diarrhea and rash more often than was aspirin. Clopidogrel had fewer serious hematological adverse effects than ticlopidine, particularly in regard to neutropenia and thrombotic thrombocytopenic purpura (TTP).
- Active-controlled trials: In the PCI-CURE[10] trial, no difference in major or minor bleeding was seen between clopidogrel and aspirin at 30 days. At 8 months of follow-up, the only statistically significant difference in bleeding for clopidogrel compared to aspirin was minor bleeding episodes (RR 1.68, 95% CI 1.06-2.68, p=0.03). In the CREDO[11] study, the reasons patients (n=99) stopped the study medications prior to PCI were not provided. Following the 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).

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.

Head-to-head trials:

Acute Coronary Syndrome (ACS)

No relevant head-to-head trials were identified.

Active-controlled trials

One active-controlled trial of good quality, Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events Trial (CURE),[8, 21] 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 300mg loading dose, 75mg 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 325mg daily in both groups (mean dose, 150mg).

All-cause and cardiovascular mortality

There were fewer deaths from cardiovascular causes, a secondary endpoint in CURE, [8] with clopidogrel than with aspirin, but this was not statistically significant (5.1% versus 5.5%; RR 0.93, 95% CI 0.80-1.10).

Combined Outcomes (fatal and non-fatal)

Two primary endpoints in CURE[8] 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%; p<0.001, RR 0.88, 95% CI 0.81-0.95). 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; p<0.01, RR 0.66, 95% CI 0.51-0.86). By 30 days, the RR for the first primary endpoint was significant for clopidogrel compared to placebo (4.3% vs. 5.4%; p=0.003, RR 0.79, 95% CI 0.67-0.92) 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 RR (18%) remained for the primary outcome (CV death, 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 to1 and 1 to 3 months compared to the other treatment periods 3 to 6, 6 to 9, and 9 to 12 months.[22]

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 ≥ 200mg (n=4110). The combined incidence of CV death, MI, or stroke (first primary outcome) was reduced from 13.6% to 9.8% (RR 0.71, 95% CI 0.69-0.85, p <0.001), with clopidogrel plus high-dose aspirin compared to high-dose aspirin alone. The incidence of the first primary end point 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.

Cardiovascular events (stroke, MI)

In CURE,[8] 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 4 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[8], 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[8] trial are included in Evidence Table A1 and Quality Table A2). Additional outcomes from the CURE[8] trial are presented in Table 4.

Table 4: Outcomes from CURE[8] 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 CV 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)
CV Mortality	318 (5.1)	345 (5.5)	0.93 (0.80-1.10)
MI†	324(5.2)	419 (6.7)	0.78 (0.68-0.90)
Q-wave	116 (1.9)	193 (3.1)	0.61 (0.48-0.76)
Non-Q wave	216 (3.5)	242 (3.8)	0.90 (0.75-1.08)
Stroke	75 (1.2)	87 (1.4)	0.87 (0.64-1.18)
Refractory ischemia*	544 (8.7)	587 (9.3)	0.93 (0.83-1.04)
During initial hospitalization§	85 (1.4)	126 (2.0)	0.68 (0.52-0.90)
After discharge¶	459 (7.6)	461 (7.6)	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)

† Some patients had both Q-wave and non-Q wave MI. ARR= absolute risk reduction. ¶ Refractory ischemia after hospital discharge = rehospitalization for unstable angina with ECG changes. §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.*Only the first ischemic event was counted for each patient. ** Patients with events other than those included in the first primary outcome while they were in the hospital. NS = not significant.

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

In CURE,[8] 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[8] from the 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.[24] 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 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[16] and two journal articles[17, 25] on four trials involving 22,656 patients. Patients with the diagnoses of a recent MI (n=3602), 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; 2, p=0.01).

Head-to-head trials-Percutaneous Coronary Intervention (PCI)

No trials with extended release dipyridamole/ASA in the setting of PCI 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[26-28] were rated poor in quality. The study conducted by Moussa et al.[27] was an observational nonrandomized comparison between the two agents in a consecutive fashion. The study conducted by Piamsomboon et al.[26] 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.[28] also had inadequate allocation concealment, and outcome assessors were not masked in the study. Both studies[26, 28] utilized doses of ASA that would no longer be used in clinical practice.

Four randomized head-to-head studies of fair quality were included in this review. The study by Atmaca et al.[29] 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.[30] 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.[31] In this study,[31] 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 0.45; p=0.003). The secondary endpoint 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.[32] 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.[32] 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. (Details of these trials are included in Evidence Table A1 and Quality Table A2.)

One head-to-head randomized controlled study[9] 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 300mg loading dose followed by clopidogrel 75mg plus ASA 325mg daily; (2) clopidogrel 75mg plus ASA 325mg daily (no loading dose); or (3) ticlopidine 250mg twice a day plus aspirin 325mg daily.

Outcomes: Head-to-head trials

The CLASSICS[9] trial was primarily a safety study. In CLASSICS, the secondary outcomes were MACE including MI (fatal and non-fatal), MI plus target lesion revascularization (TLR), and sudden death. The 30-day rate for MACE was similar between ticlopidine and clopidogrel ($p \geq 0.5$).

Active-controlled trials

The active controlled study performed by Hall et al.[33] was an open-label, randomized, unblinded univariate risk analysis of the CAPRIE[15] trial; it was judged to be of poor in quality.

Rupprecht et al.[34] randomized patients to one of three groups: (1) ticlopidine; (2) ticlopidine plus ASA 300mg; or (3) ASA 300mg. 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.[35] studied whether ASA 325mg plus ticlopidine 250mg twice a day was as effective as ASA 325mg 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.

Two active-controlled trials[10, 11] rated good in quality were included. The Percutaneous Coronary Intervention Study (PCI-CURE)[10] was a prospectively designed analysis in a subset of patients (n=2658) from the CURE[8] trial. The goal 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),[11] 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 undergoing elective PCI. The patients (n=1053) were randomized to a preprocedural loading dose of 300mg clopidogrel (3–24 hours prior to PCI, mean 9.8 hours) or placebo (n=1063) plus 325mg 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 75mg and ASA 325mg daily for 28 days. At that point, the group that received the clopidogrel loading dose continued to receive clopidogrel 75mg per day, whereas the no-pretreatment group received a matching placebo. The ASA dose after 28 days was in the range of 81 to 325mg. Drug treatment was completed at 1 year in 63% of patients in the clopidogrel group and 61% of patients in the control group.

All-cause and cardiovascular mortality

In the study conducted by Leon et al.[35] 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,[10] 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 0.52-3.45). 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 (clopidogrel 2.3%, placebo group 2.4%). (Refer to Table 5.)

In CREDO,[11] 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).

Cardiovascular events (stroke, MI)

In the Leon et al. study,[35] 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,[10] 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 (2.4% to 0.8%, 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). Stroke was not an outcome evaluated in the PCI-CURE trial. (Refer to Table 5.)

Table 5: PCI-CURE:[10] Major outcome events from PCI to 30 days and end of follow-up

	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 (18.3)	59 (4.4)	108 (21.7)	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.

In CREDO,[11] maintaining clopidogrel and ASA for one year resulted in a decrease in the composite primary endpoint (death, MI, and stroke) compared to placebo plus aspirin (8.5% vs. 11.5%; RR 0.73, 95% CI 0.57-0.95, ARR 3%, NNT=33). Numerical benefits were noted in some of the individual components, favoring clopidogrel over placebo, although these were not statistically significant (i.e., MI 6.6% vs. 8.5%, RR 0.79, 95% CI 0.58-1.06, p= 0.114; and stroke (0.9% vs. 1.1%, RR 0.76, 95% CI 0.32-1.79). (Refer to Table 6.)

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

In the Leon et al. study,[35] 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,[10] 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).

In CREDO,[11] 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); p=0.2, RR 18.5, 95% CI -14.2-41.8). 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 6: CREDO: Major outcome events at 1 year[11]

	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[19, 20] comparing the combination of ASA with clopidogrel to ASA and ticlopidine were identified. The first analysis, conducted by Bhatt et al.[20] included three

randomized trials[9, 30, 32] and seven single-center registries of which three[27, 36, 37] 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.[19] included the same three randomized trials[30, 9, 32] and six of the seven registries, of which three[36,27, 37] 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 0.64, 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 for ASA plus ticlopidine (1.2%, n=15/1207) (OR 1.05, 95% CI 0.52-2.12, p=0.9). No 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). (More details of these meta-analyses are included in Table A3–Systematic Reviews.)

In the systematic review by Tran et al.[24] 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[10] and CREDO[11] trials.

Key Question 1b. In patients with prior ischemic stroke or TIA, what is the comparative efficacy of the newer antiplatelet agents in all-cause and cardiovascular mortality, cardiovascular events (stroke, MI), 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: Four high-quality, multicenter randomized controlled trials (RCTs) were included.
  - **ERDP/ASA:** The Second European Stroke Prevention Study[12] (ESPS-2) consisted of four treatment arms: (1) extended release dipyridamole (ERDP) 200mg; (2) extended-release dipyridamole 200mg and immediate release ASA 25mg (ERDP/ASA); (3) immediate-release ASA 25mg; (4) placebo. The study had two primary efficacy endpoints: stroke (fatal or non-fatal), and death from all causes. In ESPS-2,[12] a combination of ERDP and ASA

significantly reduced the incidence of first and second strokes, recurrent TIA, and death compared to aspirin alone. In ESPS-2, ERDP had a comparable effect to aspirin. Both agents individually were less effective than a combination of ERDP and ASA. Compared with placebo, the ERDP/ASA combination was twice as effective for preventing stroke as either aspirin or extended release dipyridamole alone. 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.

- **Clopidogrel:** The MATCH[13] 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 75mg 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 75mg 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.
- **Ticlopidine:** The TASS[14] study was a North American randomized, double-blind study comparing the effect of ticlopidine 250mg twice a day to ASA 650mg 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. In TASS[14], ticlopidine was somewhat more effective than ASA 650mg in reducing the risk of death from any cause or the risk of nonfatal stroke in patients with a history of recent TIA or minor stroke, p=0.048.

- Of the RCTs with long duration, 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. No difference in the incidence of stroke (non-fatal or fatal) was observed with ticlopidine at 5 years.
- All the newer antiplatelet agents resulted in no difference in all-cause/CV mortality.
- The overall grade of evidence is good.
- Meta-analyses: Four meta-analyses were evaluated. Three of the meta-analyses[16, 25, 17, 38] 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[38] 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) study.

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[39] 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 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.

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

The study conducted by Ito et al.[40] 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.

Gorelick et al.[41] 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). 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 ASA group. The study was judged to be fair-good in quality.

The Second European Stroke Prevention Study (ESPS-2)[12, 39] consisted of four treatment arms: (1) extended release dipyridamole (ERDP) 200mg (n=1650); (2) extended-release dipyridamole 200mg and immediate-release ASA 25mg (ERDP/ASA) (n= 1650); (3) immediate-release ASA 25mg (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)[13] study was a randomized, double-blind, international study evaluating the risk of recurrent ischemic vascular events with clopidogrel plus placebo or clopidogrel plus 75mg 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)[14] was a randomized, double-blind study, conducted in North America, comparing the effect of ticlopidine 250mg twice a day to ASA 650mg 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.)

All-cause and cardiovascular mortality

Gorelick et al.[41] reported no difference in the all cause mortality with ticlopidine compared with ASA at two years.

In ESPS-2,[12, 42] 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. For 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.[12]

In MATCH,[13] death from any cause (a secondary endpoint) was similar between clopidogrel plus ASA and clopidogrel alone. (Refer to Table 7 for other outcomes.)

In TASS,[14] 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.

Cardiovascular events (stroke, MI)

Gorelick et al.[41] reported no difference in the fatal or non-fatal MI with ticlopidine compared with ASA. The incidence of recurrent stroke (fatal or non-fatal) with ticlopidine compared to ASA was not significant at 2 years.

In ESPS-2,[12] 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).[39, 42] 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).[39] 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.

The MATCH[13] 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 7 for other outcomes.)

TABLE 7: MATCH trial: Number of patients (%) with events[13]

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

* 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[14] 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 ASA (RR 0.70, 95% CI 0.37-1.32). Combining the two endpoints, the incidence was 11.2% for ticlopidine and 13.8% for ASA (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.[41] did not evaluate the endpoint of invasive vascular procedures or failures.

The endpoint of vascular procedures alone was not evaluated in ESPS-2.[39] 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,[13] 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%; RRR 6.4, 95% CI -4.6-16.3). 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.[14]

Systematic reviews

The systematic review done by Tran et al.[24] 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[16] and two journal articles[17, 25] 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[25] 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%, p=.01; OR 0.91, 95% CI 0.84 -0.98). 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[43] 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[38] combined dipyridamole plus ASA trials (14 trials with 5317 patients) from the 1994 Antiplatelet Trialists' Collaboration (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. 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.

Key Question 1c. In patients with symptomatic peripheral vascular disease what is the comparative efficacy of the newer antiplatelet agents in all-cause and cardiovascular mortality, cardiovascular events (stroke, MI), 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[15] (RCT) was included.
  - The CAPRIE[15] study compared clopidogrel 75mg to ASA 325 mg daily for reducing the risk of future thrombotic events (MI, stroke, or vascular disease). Three subsets of patients, including those with a history of recent ischemic stroke, MI, or established PAD, were enrolled. The study found 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). For patients with stroke specifically, clopidogrel and aspirin had similar outcomes in CAPRIE, but the statistical power was insufficient to exclude a small difference in treatment effect in the ischemic stroke subset of patients as well as the other clinical 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. Therefore, subgroup analyses should be interpreted with caution. One such analysis found that PVD patients 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). The percentage of patients that permanently discontinued the study drug early was 21.2% for reasons other than the occurrence of an outcome event.

Safety/Adverse Events:

- In the CAPRIE[44] 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%).

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

One matched-controlled trial[45] (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.

The Clopidogrel vs. ASA in Patients at Risk for Ischemic Events (CAPRIE)[15] trial compared clopidogrel 75mg to placebo 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.)

All-cause and cardiovascular mortality

In CAPRIE,[15] 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%). However, for the combined endpoint of ischemic stroke, MI, and vascular death, an intention-to-treat analysis resulted in an ARR of .51% and a RRR of 8.7% (95% CI 0.3-16.5, p=0.0430) at 36 months in favor of clopidogrel. (Additional outcomes from the CAPRIE trial are depicted in Table 8.)

Table 8: CAPRIE[15] trial: Comparison of outcome event cluster rates

Primary outcome event cluster	Clopidogrel + ASA Event rate per year,%	Placebo + ASA Event rate per year, %	Relative Risk (95% CI) P value
Ischemic stroke, MI or vascular death	5.32	5.83	0.91 (0.84-1.00) 0.043
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, amputation, or vascular death	6.43	6.90	0.94 (0.87-1.01) NS
Death from any cause	3.05	3.11	0.98(0.88 to 1.10) NS

† Includes primary intracranial hemorrhage. NS = Not Significant

Cardiovascular events (stroke, MI)

Stroke as an independent endpoint was not included in CAPRIE.[15] (Refer to Table 8 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.)

In CAPRIE, a subgroup analysis[46] 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[47, 48-50] 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,[15] 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[24] 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.[51] 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.[51] 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. For adults with acute coronary syndromes or coronary intervention procedures, 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[16, 17, 25] and multiple large, randomized controlled trials including CURE,[8] PCI-CURE,[10] CREDO,[11] CLASSICS,[9] MATCH,[13] TASS,[14] ESPS-2,[39] and CAPRIE.[15] 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[39] trial. Clopidogrel was evaluated in more than 17,500 patients including over 9,000 treated for 1 year or more (CAPRIE[15] and CURE[8] trials). Ticlopidine was evaluated in more than 4000 patients for 5 years in the TASS[14] and the Canadian American Ticlopidine Study (CATS)[52] trials. The CATS[52] 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.)

Serious adverse events reported

In the CURE[8] trial, major bleeding was statistically more frequent with clopidogrel and aspirin than with 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 occurred early in the study. Within 30 days of randomization, the rate of major bleeding with clopidogrel was 2.0% and 1.5% with 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 9.)

In the CURE[8] 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 aspirin alone (n=137, 2.2%, p=0.02). The investigators reported that for every 1000 patients treated with clopidogrel for a mean of 9 months, 6 would require a blood transfusion.

TABLE 9: CURE: Incidence of all types of bleeding per months of therapy[53]

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)	144/168 (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[8] 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 ≤ 100mg, 1.9%; ASA 101-199mg, 2.8%; ASA ≥ 200mg, 3.7%; p=0.0001) and the clopidogrel group (ASA ≤ 100mg, 3.0%; ASA 101-199mg, 3.4%; ASA ≥ 200mg, 4.9%; p=0.0009). (Refer to Table 10.) 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,[8] 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 1.10-1.99). Most of the patients scheduled for CABG discontinued the study medication 5 days before the procedure. The subset of patients (n=912) discontinuing clopidogrel during the 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 10: CURE:[8, 23] Percentage of major and life-threatening bleeding per aspirin dose

Bleeding complications	ASA	ASA + Clopidogrel	All patients
*Major**			
ASA ≤ 100mg (n=5320)	1.86	2.97	2.41
ASA 101-199mg (n=3109)	2.82	3.41	3.12
ASA ≥ 200mg (n=4110)	3.67	4.86	4.26
p-value for trend	<0.0001	<0.001	<0.0001
*Life-threatening***			
ASA ≤ 100mg (n=5320)	1.26	1.75	1.50
ASA 101-199mg (n=3109)	1.90	1.39	1.64
ASA ≥ 200mg (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[10] trial, no difference in major or minor bleeding was seen between clopidogrel and aspirin 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 CAPRIE[15, 44] 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 severe intracranial hemorrhage (0.5% to 0.4%) and severe indigestion/nausea/vomiting (17.6% vs. 15.0%) was higher with aspirin than clopidogrel, but not significantly so. The frequency of severe diarrhea was higher with clopidogrel than aspirin, though not significantly so (4.5% vs. 3.5%; p=0.056).

A randomized study[34] compared the antiplatelet effects after stent implantation in 61 patients using three different treatment arms over 2 weeks: Group A (ticlopidine 500mg plus ASA 300mg per day); Group B (ticlopidine 500mg monotherapy); or Group C (ASA 300mg per day). One major bleeding event occurred in one patient from Group C, with that patient's hemoglobin dropping by 4mg/dL due to a groin hemorrhage. No blood transfusion was required.

In the ESPS-2[39] trial, 430/6602 patients reported at least one adverse bleeding event during the 2-year follow-up period. Most patients (279/430 or 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.

In MATCH[13] trial, adding aspirin to clopidogrel resulted in significantly more bleeding complications compared 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 ≥ 2 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 TASS[14] 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.[35] 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[18] evaluated whether high-risk patients (n=320, mean age 72 years) presenting with a upper GI bleed on ≤ 325mg of ASA would have fewer subsequent bleeding episodes on clopidogrel 75mg or aspirin 80mg 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[39] 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.[54] 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 <100mg and 20 trials with ASA ≥ 100mg). 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 100mg had similar rates of hemorrhagic events compared with the thienopyridines. (Refer to Table 11.)

Table 11: Meta-analysis:[54] Frequency of bleeding complications per antiplatelet class and dose

Bleeding type	No. of trials reported	No. of patients	% Rate (95% CI)
Major bleeding			
ASA <100mg	5	13,337	1.7 (1.4-1.9)
ASA 100-325mg	11	43,489	1.7 (1.5-1.8)
ASA >325mg	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 <100mg	3	11,963	1.8,(1.5-2.0)
ASA 100-325mg	5	13,588	6.5,(6,1-6.9)
ASA >325mg	0		
Thienopyridines	1	6,259	5.1 (4.6-5.7)
Hemorrhagic bleed			
ASA <100mg	4	12,661	0.3,(0.2-0.4)
ASA 100-325mg	15	152,955	0.3,(0.2-0.3)
ASA >325mg	3	2,224	1.1,(0.7-1.5)
Thienopyridines	2	15,858	0.3,(0.2-0.3)
GI bleed			
ASA <100mg	5	13,337	1.1,(0.9-1.3)
ASA 100-325mg	7	30,413	2.4,(2.2-2.6)
ASA >325mg	3	2,224	2.5 (1.8-3.1)
Thienopyridines	5	17,824	1.6 (1.4-1.8)
TOTAL			
ASA <100mg	4	12,639	3.6,(3.3-3.9)
ASA 100-325mg	6	22,745	9.1,(8.7-9.4)
ASA >325mg	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

Neutropenia

Infrequent but important hematological adverse effects of ticlopidine include neutropenia, agranulocytosis, aplastic anemia, pancytopenia, thrombotic thrombocytopenic purpura, and thrombocytopenia. One review article,[55] 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 hematolological disorders more often.

In the TASS[14] 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[52] trial, using the same definition of neutropenia and severe neutropenia as in the TASS[14] 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[52] 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[52] and TASS[14] suggests a 2.4% incidence for neutropenia and a 0.85% incidence for severe neutropenia and agranulocytosis with ticlopidine.[55]

In contrast, in STARS[56] and ISAR,[57] 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,[44] 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,[8] the rates of neutropenia in the number of patients with neutropenia (3 on clopidogrel plus aspirin vs. 3 on aspirin alone) and thrombocytopenia (19 clopidogrel plus aspirin vs. 24 aspirin alone) were similar.[6] No cases of TTP were reported.

The study by Leon et al.[35] 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.[55] Between the years of 1992 and 1997, 119 cases of ticlopidine-induced TTP were reported to the FDA MedWatch Program.[58] Typically, ticlopidine-induced TTP occurs 2 to12 weeks after treatment is initiated.

Based on available evidence, the estimated incidence of TTP ranges from about 1 case per 1600 to 5000,[59] with a mortality rate of 33%.[60]

Bennett et al.[60] 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.[59] 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.[6]

Overall adverse effect reports

Aspirin itself is well known to increase 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[8] trial, GI events (abdominal pain, dyspepsia, gastritis, and constipation) were higher

with ASA than clopidogrel (12.5% vs. 11.7%). In the CAPRIE[44] 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 0.5% of the time with clopidogrel and 0.4% with ASA.

Hankey and colleagues reported in a Cochrane Review[16] and two journal articles[17, 25] on four trials of thienopyridines and ASA use in 22,656 patients at high risk for vascular disease. Two trials,[14, 15] 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 12.)

Table 12: Meta-analyses:[16,17, 25] Comparing the incidence of adverse events with thienopyridines with 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	5.6	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.[17]
†provided by Hankey et al.[25]

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 above.) Diarrhea and rash are more common with the thienopyridines, particularly with ticlopidine, than with aspirin.

In the CURE[8] trial, rash and other skin disorders were the most common adverse reaction with clopidogrel compared to ASA (4.0% vs. 3.5%; $p \leq 0.05$). In the Cochrane meta-analysis,[16] 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,[15] 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).[6]

In the ESPS-2[39] 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 13.) Headache occurred 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.

In the TASS[14] 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 13: ESPS-2:[12,39] 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	32.2
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	15.5	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.

META-ANALYSIS OF SPECIFIC ADVERSE EVENTS: COMPARISONS 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 Table 14, 15, and 16.

Table 14 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 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 14. Adverse event analysis at patient level: Antiplatelet agents vs. aspirin

Adverse events	Drug	# of trials	Aspirin		Intervention groups		Pooled OR	95% CI
			# people with event	sample size	# people with event	sample size		
Minor bleeding	Clopidogrel	1	153	6303	322	6259	2.18	(1.79, 2.67)
Minor bleeding	Clopidogrel + Aspirin	1	59	1063	56	1053	0.96	(0.64, 1.42)
Minor bleeding	Dipyridamole	0	NR	NR	NR	NR	NC	NC
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	1	71	1063	93	1053	1.35	(0.97, 1.89)
Major bleeding	Dipyridamole	0	NR	NR	NR	NR	NC	NC
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
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)

Adverse events	Drug	# of trials	Aspirin		Intervention groups		Pooled OR	95% CI
			# people with event	sample size	# people with event	sample size		
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
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 15, trials comparing ticlopidine to clopidogrel are summarized. No statistically significant differences were observed in the rate of adverse events, although 95% confidence intervals are wide, so we cannot conclude that there is no difference.

Table 15. Adverse Event Analysis at Patient Level: Ticlopidine vs. Clopidogrel

Adverse events	# of trials	Ticlopidine		Clopidogrel		Pooled OR	95% CI
		# people with event	sample size	# people with event	sample size		
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 16 presents the summary of adverse events of trials comparing ticlopidine and aspirin to clopidogrel and aspirin. As with Table 15, no differences were seen, but wide confidence intervals mean that no strong conclusions can be drawn.

Table 16. Adverse events analysis at patient level: 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	1	0	31	2	37	Inf+	(0.16, +Inf)
Major bleeding	1	1	31	2	37	1.70	(0.08, 104.46)
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	3	74	1888	14	790	0.57	(0.29, 1.06)
Rash	1	1	1919	11	827	0.32	(0.15, 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.

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.[9, 32] In Taniuchi et al.[32] 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[9] 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). Skin disorders, primarily rash, were the most frequent reason for discontinuing therapy, with incidences of 2.6% in ticlopidine users and 0.6% in clopidogrel users. One ticlopidine patient (0.3%) developed neutropenia (neutrophil <0.1 x 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[8] trial, 21.1% of the patients in the clopidogrel group discontinued the study medication permanently, compared to 18.8% in the aspirin group (p=0.001). The discontinuation rates due to adverse events were comparable between clopidogrel and aspirin. Minor bleeding (defined as other hemorrhages requiring interruption of the drug regimen) was significant with clopidogrel (5.1% vs. 2.4%; p<0.001).

In the CREDO[11] study, the reasons patients (n=99) stopped the study medications prior to PCI 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 the ESPS-2[39] 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 (132/219) and 38% (46/121) in the non-ERDP groups.

In the CAPRIE[44] 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[14] 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.

Key Question 3. 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,[8] clopidogrel 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 (7.6% vs. 5.4%).

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.[6]

A separate analysis of the ESPS-2[61] 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[62] 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[41] 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[8] 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%).

No significant difference was observed in the plasma level of the main circulating metabolite of clopidogrel between males and females.[6] 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,[14] 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[12] trial, 42% of the study population was women. No gender difference in efficacy or tolerability was noted.

Comorbidities

In a subset analysis[8] of CURE, patients with diabetes had a lower incidence of the first primary outcome on clopidogrel than placebo (16.7 % to 14.2%). Likewise, patients without diabetes also had a lower incidence of the first primary outcome with clopidogrel than placebo (9.9 to 7.9%). Diabetes had higher event rates than non-diabetics but within the diabetic group, those on clopidogrel showed a benefit compared to placebo.

The CAPRIE[15] trial was not powered to detect overall differences between the 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 17.)

Table 17: Results of CAPRIE:[15] 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[63] on 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)[64] suggested that the 8.7% relative risk reduction 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[65] 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, 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, myocardial infarction, 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[46] 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[5] 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 18.) However, comparative statistics within subgroups were not provided.

Table 18: ESPS-2 trial:[5] 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

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[21] 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 2b/3a antagonist, beta-blockers, ACE inhibitors, lipid-lowering agents, calcium channel blockers and intravenous nitrate.

A poster abstract[66] using CAPRIE data suggested that patients on various medications in the clopidogrel and ASA group experienced no differences in adverse events. These medications included ACE inhibitors, antidiabetics, anti-epileptic, beta-blockers, calcium channel blockers, coronary vasodilators, diuretics, peripheral vasodilators, lipid-lowering agents, and GP2b/3a agents. There was no evidence that concurrent use of these drugs lead to different adverse consequences. However, all the newer 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. [6]

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. [67]

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. [68]

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[6] is summarized in Appendix E for clopidogrel.

Information from the literature provided by the manufacturer[5] 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[67] 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. [67, 69] 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. [68]

Table 19. Summary of the Evidence by Key Question

Key Question 1: Efficacy	Quality of Evidence	Conclusion
ACS: 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)	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. Clopidogrel (one active-controlled trial) reduced all-cause/CV mortality (secondary endpoint) but not significantly compared to placebo at 12 months, (mean duration 9 months). Clopidogrel in combination with ASA significantly reduced the first primary endpoint of death from CV causes including nonfatal MI and CVA 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, CVA and refractory ischemia, p<0.001. The incidence of MI for clopidogrel vs. placebo was 5.2% vs. 6.7%, p=0.001, NNT=67 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.
Coronary Intervention Procedures: 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)	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). Five active controlled trials were evaluated. Two trials were rated poor. One trial was rated as fair .The other two trials (PCI-CURE and CREDO) were rated good in quality. **Clopidogrel vs. Ticlopidine (Head-to-Head-CLASSICS trial)**: This study was primarily a safety study. No difference was seen for major adverse clinical events (death, MI, target lesion revascularization) at 30 days between the two agents. Cardiovascular events (stroke, MI) and invasive procedure failure were not reported in this trial. **Clopidogrel: (two active-controlled trials):** PCI-CURE trial: Cardiovascular death at 30 days post PCI and at 1 year was not statistically different with clopidogrel compared to placebo. The composite endpoint of cardiovascular death and MI was statistically significant, p =0.002 with clopidogrel compared to placebo at 1 year. 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 was seen at 30 days. The incidence of the composite endpoints of nonfatal MI, urgent target vessel revascularization and 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 was18.3% 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 different. The composite primary endpoint (death , MI, 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.

Stroke/TIA: comparative efficacy on all-cause and CV mortality, CV events (stroke, MI) invasive vascular procedure failure (including need for additional invasive vascular procedures	ERDP/ASA (good) clopidogrel (good) ticlopidine (good)	No head-to-head trials comparing newer antiplatelet agents in stroke/TIA. **ERDP/ASA** (one active-controlled trial) ESPS-2 trial: No difference in all cause mortality (primary endpoint) with ERDP/ASA compared to ERDP vs. ASA vs. placebo. 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. **Clopidogrel**: (two active-controlled trials) MATCH trial: No difference in death from any cause with clopidogrel plus ASA compared to clopidogrel alone during 18 months of follow-up. No difference was seen either between the two groups for ischemic stroke (fatal or non-fatal); composite ischemic strokes, MI or vascular death; MI (fatal or non-fatal). The combination of aspirin plus clopidogrel was no more effective than clopidogrel alone in the composite primary endpoint including rehospitalization for acute ischemic events (unstable angina pectoris, worsening of PAD requiring therapeutic intervention, urgent revascularization or TIA). **Ticlopidine-**(one active-controlled trial) TASS trial: Ticlopidine 250mg twice a day was slightly more effective than ASA 650mg 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.
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 placebo at 36 months. A significant difference for the combined endpoint of stroke, MI and vascular death at 36 months was observed between clopidogrel and aspirin; RRR 8.7% (95% CI 0.3-16.5); p=0.043. Clopidogrel did decrease the incidence of AMI at 36 months compared to ASA, p=0.008. The cluster endpoint of amputation with 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:** 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. **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 100mg/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 (1.37% vs. 0.7% vs. placebo) and bleeding at arterial puncture sites. The incidence of bleeding decreased over the duration of the study. • 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: 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). • 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. Major or minor bleeding rates were not reported or defined.

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 by 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 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, GP2b/3a, 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 with other medications.

REFERENCES

1. American Heart Association. American Heart Association homepage. Available at URL: http://www.americanheart.org. Accessed 3/2005.

2. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction--2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). Circulation 2002;106(14):1893-900.

3. Bertrand ME, Simoons ML, Fox KA, et al. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2002;23(23):1809-40.

4. Popma JJ, Berger P, Ohman EM, et al. Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(3 Suppl):576S-599S.

5. Boehringer Ingelheim Pharmaceuticals. Formulary submission dossier for Aggrenox (aspirin/extended-release dipyridamole 25mg/200mg). Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals. 2001.

6. Bristol Myers Squibb/Sanofi Partnership. Plavix (clopidogrel bisulfate): formulary submission dossier.: Bristol Myers Squibb/Sanofi Partnership. 2004.

7. Version 4.0.1. Cambridge, MA: 2004.

8. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345(7):494-502.

9. 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.

10. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358(9281):527-33.

11. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288(19):2411-20.

12. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996;143(1-2):1-13.

13. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364(9431):331-7.

14. Hass WK, Easton JD, Adams HP Jr, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. N Engl J Med 1989;321(8):501-7.

15. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348(9038):1329-39.

16. Hankey GJ, Sudlow CL, Dunbabin DW. Thienopyridine derivatives (ticlopidine, clopidogrel) versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. Cochrane Database Syst Rev 2000;(2):CD001246 .

17. Hankey GJ, Sudlow CL, Dunbabin DW. Thienopyridines or aspirin to prevent stroke and other serious vascular events in patients at high risk of vascular disease? A systematic review of the evidence from randomized trials. Stroke 2000;31(7): 1779-84.

18. 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.

19. Casella G, Ottani F, Pavesi PC, et al. Safety and efficacy evaluation of clopidogrel compared to ticlopidine after stent implantation: an updated meta-analysis. Ital Heart J 2003;4(10):677-84.

20. Bhatt DL, Bertrand ME, Berger PB, et al. Meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting. J Am Coll Cardiol 2002;39(1):9-14.

21. Mehta SR, Yusuf S. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. Eur Heart J 2000;21(24):2033-41.

22. Yusuf S, Mehta SR, Zhao F, et al. Early and late effects of clopidogrel in patients with acute coronary syndromes. Circulation 2003;107(7):966-72.

23. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation 2003;108(14):1682-7.

24. Tran H, Anand SS. Oral antiplatelet therapy in cerebrovascular disease, coronary artery disease, and peripheral arterial disease. JAMA 2004;292(15):1867-74.

25. Hankey GJ, Sudlow CLM, Dunbabin DW, et al. Regular or "super-aspirins"? A review of thienopyridines or aspirin to prevent stroke. J Am Geriatr Soc 2001;49(4):487-489.

26. Piamsomboon C, Laothavorn P, Chatlaong B, et al. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin after coronary stent implantation: 1 and 6-month follow-up. J Med Assoc Thai 2001;84(12):1701-7.

27. Moussa I, Oetgen M, Roubin G, et al. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. Circulation 1999;99(18):2364-6.

28. Juergens CP, Wong AM, Leung DY, et al. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after coronary stent implantation. Am Heart J 2004;147(4):E15.

29. Atmaca Y, Dandachi R, Gulec S, et al. Comparison of clopidogrel versus ticlopidine for prevention of minor myocardial injury after elective coronary stenting. Int J Cardiol 2003;87(2-3):143-9.

30. Muller C, Buttner HJ, Petersen J, et al. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. Circulation 2000;101(6):590-3.

31. Mueller C, Roskamm H, Neumann FJ, et al. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary artery stents. J Am Coll Cardiol 2003;41(6):969-73.

32. Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. Circulation 2001;104(5):539-43.

33. Hall P, Nakamura S, Maiello L, et al. A randomized comparison of combined ticlopidine and aspirin therapy versus aspirin therapy alone after successful intravascular ultrasound-guided stent implantation. Circulation 1996;93(2):215-22.

34. Rupprecht HJ, Darius H, Borkowski U, et al. Comparison of antiplatelet effects of aspirin, ticlopidine, or their combination after stent implantation. Circulation 1998;97(11):1046-52.

35. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med 1998;339(23):1665-71.

36. Mishkel GJ, Aguirre FV, Ligon RW, et al. Clopidogrel as adjunctive antiplatelet therapy during coronary stenting. J Am Coll Cardiol 1999;34(7):1884-90.

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

38. Wilterdink JL, Easton JD. Dipyridamole plus aspirin in cerebrovascular disease. Arch Neurol 1999;56(9):1087-92.

39. European Stroke Prevention Study 2. Efficacy and safety data. J Neurol Sci 1997;151 Suppl:S1-77.

40. Ito E, Takahashi A, Yamamoto H, et al. Ticlopidine alone versus ticlopidine plus aspirin for preventing recurrent stroke. Internal Medicine 2003;42(9):793-799.

41. Gorelick PB, Richardson D, Kelly M, et al. Aspirin and ticlopidine for prevention of recurrent stroke in black patients: a randomized trial. JAMA 2003;289(22):2947-57.

42. Forbes CD. Secondary stroke prevention with low-dose aspirin, sustained release dipyridamole alone and in combination. ESPS Investigators. European Stroke Prevention Study. Thromb Res 1998;92(1Suppl 1):S1-6.

43. 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.

44. Harker LA, Boissel JP, Pilgrim AJ, et al. Comparative safety and tolerability of clopidogrel and aspirin: results from CAPRIE. CAPRIE Steering Committee and Investigators. Clopidogrel versus aspirin in patients at risk of ischaemic events. Drug Saf 1999;21(4):325-35.

45. Fiotti N, Altamura N, Cappelli C, et al. Long term prognosis in patients with peripheral arterial disease treated with antiplatelet agents. Eur J Vasc Endovasc Surg 2003;26(4):374-80.

46. 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.

47. Hacke W. On behalf of the CAPRIE I. Consistency of the benefit of clopidogrel over aspirin in patients wth lacunar and non-lacunar stroke. Cerebrovasc Dis 1998;8(Suppl 4):51.

48. Gent M. Benefit of clopidogrel in patients with coronary disease. Circulation 1997;96(Suppl1):467.

49. Bhatt D, Foody J, Hirsch A, et al. Complementary, additive benefit of clopidogrel and lipid-lowering therapy in patients with atherosclerosis. J Am Coll Cardiol 2000;35(Suppl A):326.

50. Rupprecht HJ. Consistency of the benefit of clopidogrel across a range of vascular-related endpoints: results from CAPRIE. Eur Heart J 1998;19(Suppl): Abstract P484.

51. Robless P, Mikhailidis DP, Stansby G. Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease. Br J Surg 2001;88(6):787-800.

52. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Lancet 1989;1(8649): 1215-20.

53. Main C, Palmer S, Griffin S, et al. Assessment Report: A rapid and systematic review of the clinical effectiveness and cost effectiveness of clopidogrel used in combination with aspirin compared to aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes (ACS). 2004: University of York. York, England.

54. Serebruany VL, Malinin AI, Eisert RM, et al. Risk of Bleeding Complications with Antiplatelet Agents: Meta-Analysis of 338,191 Patients Enrolled in 50 Randomized Controlled Trials. Am J Hematol 2004;75(1):40-47.

55. Love BB, Biller J, Gent M. Adverse haematological effects of ticlopidine. Drug Saf 1998;19(2):89-98.

56. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334(17):1084-9.

57. Kastrati A, Schuhlen H, Hausleiter J, et al. Restenosis after coronary stent placement and randomization to a 4-week combined antiplatelet or anticoagulant therapy: six-month angiographic follow-up of the Intracoronary Stenting and Antithrombotic Regimen (ISAR) Trial. Circulation 1997;96(2):462-7.

58. Bhatt DL, Kapadia SR, Bajzer CT, et al. Dual antiplatelet therapy with clopidogrel and aspirin after carotid artery stenting. J Invasive Cardiol 2001;13(12):767-71.

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

60. 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.

61. Sivenius J, Cunha L, Diener HC, et al. Second European Stroke Prevention Study: antiplatelet therapy is effective regardless of age. ESPS2 Working Group. Acta Neurol Scand 1999;99(1):54-60.

62. Quilliam BJ, Lapane KL, Eaton CB, et al. Effect of antiplatelet and anticoagulant agents on risk of hospitalization for bleeding among a population of elderly nursing home stroke survivors. Stroke 2001;32(10):2299-304.

63. Ringleb PA, Bhatt DL, Hirsch AT, et al. Benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events. Stroke 2004;35(2):528-32.

64. 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.

65. 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.

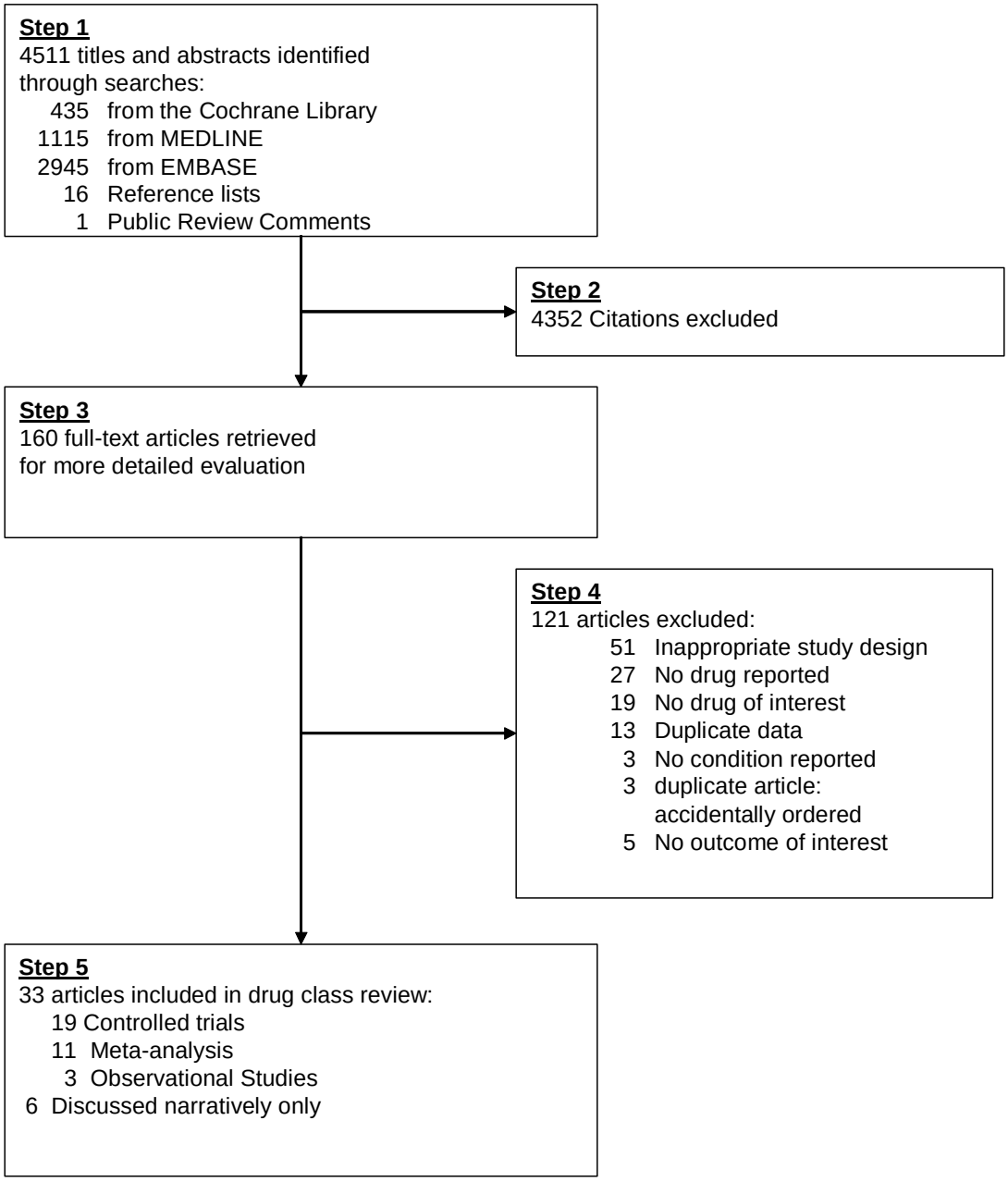
66. Morais J. Use of concomitant medications in the CAPRIE trial: clopidogrel is unlikely to be associated with clinically significant drug interactions. Eur Heart J 1998;19(Abstr 182).

67. Roche Pharmaceuticals I. Ticlid (ticlopidine hydrochloride) package insert. Nutley, NJ: Roche Pharmaceuticals, Inc. 2001.

68. Boehringer Ingelheim Pharmaceuticals I. Aggrenox (aspirin/extended-release dipyridamole) package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2001.

69. Pharmaceuticals I. Plavix (clopidogrel bisulfate) package insert. Morrisville, NC: Pharmaceuticals, Inc. 2002.

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

Appendix C. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

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 weekdays

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 Cardiol. 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.

33. Claeys MJ, Van Der Planken MG, Michiels JJ, et al. Comparison of antiplatelet effect of loading dose of clopidogrel versus abciximab during coronary intervention. Blood Coagul Fibrinolysis 2002;13(4):283-8.

34. Coccheri S. Distribution of symptomatic atherothrombosis and influence of atherosclerotic disease burden on risks of secondary ischaemic events: results from CAPRIE. Eur Heart J 1998;19(Suppl):227.

35. Collet JP, Montalescot G, Blanchet B, et al. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. Circulation 2004;110(16):2361-2367.

36. Collins TC, Souchek J, Beyth RJ. Benefits of antithrombotic therapy after infrainguinal bypass grafting: A meta-analysis. Am J Med 2004;117(2):93-99.

37. Connolly DL, Lip GYH, Chin BSP . ABC of antithrombotic therapy: Antithrombotic strategies in acute coronary syndromes and percutaneous coronary interventions. BMJ. 2002;325(7377):1404-1407.

38. Cosmi B, Rubboli A, Castelvetri C, et al. Ticlopidine versus oral anticoagulation for coronary stenting. Cochrane Database Syst Rev 2001;(4):CD002133.

39. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. Circulation 2001;103(15):1967-71.

40. De Schryver EL, Algra A, van Gijn J. Cochrane review: dipyridamole for preventing major vascular events in patients with vascular disease. Stroke 2003;34(8):2072-80.

41. Diener HC. Dipyridamole trials in stroke prevention. Neurology 1998;51(3 Suppl 3):S17-9.

42. Diener HC, Bogousslavsky J, Brass LM, et al. Management of atherothrombosis with clopidogrel in high-risk patients with recent transient ischaemic attack or ischaemic stroke (MATCH): study design and baseline data. Cerebrovasc Dis 2004;17(2-3):253-61.

43. Dippel DW. The results of CAPRIE, IST and CAST. Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events. International Stroke Trial. Chinese Acute Stroke Trial. Thromb Res 1998;92(1 Suppl 1):S13-6.

44. Dorffler-Melly J, Buller HR, Koopman MM, et al. Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery. Cochrane Database Syst Rev 2003;(4):CD000536.

45. Duran E, Canbaz S, Ege T, et al. Aspirin versus clopidogrel for synthetic graft patency after peripheral arterial bypass grafting. Platelets 2001;12(8):503-4.

46. Easton JD. Benefit of clopidogrel in patients with evidence of cerebrovascular disease. Neurology 1998;50:PO3081.

47. Edmondson RA , Cohen AT, Das SK, et al. Low-molecular weight heparin versus aspirin and dipyridamole after femoropopliteal bypass grafting. Lancet 1994;344(8927):914-8.

48. Elsner M, Peifer A, Drexler M, et al. Clinical outcome at six months of coronary stenting followed by ticlopidine monotherapy. Am J Cardiol 1998;81(2):147-51.

49. Englberger L, Faeh B, Berdat PA, et al. Impact of clopidogrel in coronary artery bypass grafting. Eur J Cardiothorac Surg 2004;26(1):96-101.

50. Fisher LD, Gent M, Buller HR. Active-control trials: how would a new agent compare with placebo? A method illustrated with clopidogrel, aspirin, and placebo. Am Heart J 2001;141(1):26-32.

51. Forbes CD. Secondary stroke prevention with low-dose aspirin, sustained release dipyridamole alone and in combination. ESPS Investigators. European Stroke Prevention Study. Thromb Res 1998;92(1 Suppl 1):S1-6.

52. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Lancet 1989;1(8649): 1215-20.

53. Gerschutz GP, Bhatt DL. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study: to what extent should the results be generalizable? Am Heart J 2003;145(4):595-601.

54. Girolami B, Bernardi E, Prins MH, et al. Antiplatelet therapy and other interventions after revascularisation procedures in patients with peripheral arterial disease: a meta-analysis. Eur J Vasc Endovasc Surg 2000; 19(4):370-80.

55. Hacke W, Hirsch AT, Topol EJ. The benefit of clopidogrel over aspirin is amplified in high-risk subgroups with a prior history of ischaemic events. Eur Heart J 1999;20:abstract supplement.

56. Hankey G. The risk of vascular ischaemic events in patients with various clinical manifestations of atherothrombosis: data from CAPRIE. Cerebrovas Dis 1998;8:30.

57. Hankey GJ. Clopidogrel and thrombotic thrombocytopenic purpura. Lancet 2000 ;356(9226):269-70.

58. Harker LA, Boissel JP, Pilgrim AJ, et al. Comparative safety and tolerability of clopidogrel and aspirin: results from CAPRIE. CAPRIE Steering Committee and Investigators. Clopidogrel versus aspirin in patients at risk of ischaemic events. Drug Saf 1999;21(4):325-35.

59. Helft G, Osende JI, Worthley SG, et al. Acute antithrombotic effect of a front-loaded regimen of clopidogrel in patients with atherosclerosis on aspirin. Arterioscler Thromb Vasc Biol 2000;20 (10):2316-21.

60. Hoffmann R, Takimoglu-Boerekci M, Langenberg R, et al. Randomized comparison of direct stenting with predilatation followed by stenting on vessel trauma and restenosis. Am Heart J 2004;147(4).

61. Hongo RH, Ley J, Dick SE, et al. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. J Am Coll Cardiol 2002;40(2):231-7.

62. Ip RJ, Korban E, Tepper D. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin versus after the placement of coronary artery stents. Cardiovasc Rev Rep 2003;24(5):283-284.

63. Jauhar R, Bergman G, Savino S, et al. Effectiveness of aspirin and clopidogrel combination therapy in coronary stenting. Am J Cardiol 1999;84(6):726-8, A8.

64. Kamishirado H, Inoue T, Mizoguchi K, et al. Randomized comparison of cilostazol versus ticlopidine hydrochloride for antiplatelet therapy after coronary stent implantation for prevention of late restenosis. Am Heart J 2002;144(2):303-8.

65. Karabulut H, Toraman F, Evrenkaya S, et al. Clopidogrel does not increase bleeding and allogenic blood transfusion in coronary artery surgery. Eur J Cardiothorac Surg 2004;25(3):419-23.

66. Kastrati A, Schomig A, Dirschinger J, et al. A randomized trial comparing stenting with balloon angioplasty in small vessels in patients with symptomatic coronary artery disease. ISAR-SMART Study Investigators. Intracoronary Stenting or Angioplasty for Restenosis Reduction in Small Arteries. Circulation 2000;102(21):2593-8.

67. Kastrati A, Schuhlen H, Hausleiter J, et al. Restenosis after coronary stent placement and randomization to a 4-week combined antiplatelet or anticoagulant therapy: six-month angiographic follow-up of the Intracoronary Stenting and Antithrombotic Regimen (ISAR) Trial. Circulation 1997;96(2):462-7.

68. Khot UN, Nissen SE. Is CURE a cure for acute coronary syndromes? Statistical versus clinical significance. J Am Coll Cardiol 2002;40(2):218-9.

69. Leavey SF, Weinberg J. Thrombotic thrombocytopenic purpura associated with ticlopidine therapy. J Am Soc Nephrol 1997;8(4):689-93.

70. Love BB, Biller J, Gent M. Adverse haematological effects of ticlopidine. Drug Safety 1998;19(2):89-98.

71. Lowenthal A, Buyse M. Secondary prevention of stroke: does dipyridamole add to aspirin? Acta Neurol Belg 1994;94(1):24-34.

72. Machraoui A, Germing A, Lindstaedt M, et al. Efficacy and safety of ticlopidine monotherapy versus ticlopidine and aspirin after coronary artery stenting: follow-up results of a randomized study. J Invasive Cardiol 2001;13(6):431-6.

73. MacWalter RS, Shirley CP. A benefit-risk assessment of agents used in the secondary prevention of stroke. Drug Saf 2002;25(13):943-63.

74. Maier C, Gleim M, Weiss T, et al. Severe bleeding following lumbar sympathetic blockade in two patients under medication with irreversible platelet aggregation inhibitors. Anesthesiology 2002;97(3):740-3.

75. Mathew V, Berger PB, Lennon RJ, et al. Comparison of percutaneous interventions for unstable angina pectoris in patients with and without previous coronary artery bypass grafting. Am J Cardiol. 2000;86(9):931-937.

76. Markus HS, Droste DW, Kaps M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation 2005;111(17):2233-40

77. Mehta SR, Yusuf S. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. Eur Heart J 2000;21(24):2033-41.

78. Mishkel GJ, Aguirre FV, Ligon RW, et al. Clopidogrel as adjunctive antiplatelet therapy during coronary stenting. J Am Coll Cardiol 1999;34(7):1884-90.

79. Mitka M. Results of CURE trial for acute coronary syndrome. JAMA 2001;285(14):1828-9.

80. Mulder BJ, van der Doef RM, van der Wall EE, et al. Effect of various antithrombotic regimens (aspirin, aspirin plus dipyridamole, anticoagulants) on the functional status of patients and grafts one year after coronary artery bypass grafting. Eur Heart J 1994;15(8):1129-34.

81. Nacul FE, de Moraes E, Penido C, et al. Massive nasal bleeding and hemodynamic instability associated with clopidogrel. Pharm World Sci 2004;26(1):6-7.

82. Nagaoka N, Matsubara T, Okazaki K, et al. Comparison of ticlopidine and cilostazol for the prevention of restenosis after percutaneous transluminal coronary angioplasty. Jpn Heart J 2001;42(1):43-54.

83. Nair GV, Davis CJ, McKenzie ME, et al. Aspirin in patients with coronary artery disease: is it simply irresistible? J Thromb Thrombolysis 2001;11(2):117-26.

84. Pache J, Kastrati A, Mehilli J, et al. Clopidogrel therapy in patients undergoing coronary stenting: value of a high-loading-dose regimen. Catheter Cardiovasc Interv 2002;55(4):436-41.

85. Page Y, Tardy B, Zeni F, et al . Thrombotic thrombocytopenic purpura related to ticlopidine. Lancet 1991;337(8744):774-6.

86. Park SW, Lee CW, Kim HS, et al . Comparison of cilostazol versus ticlopidine therapy after stent implantation. Am J Cardiol 1999;84(5):511-4.

87. Pasqualini L , Pirro M, Lombardini R, et al. A human model of platelet-leukocyte adhesive interactions during controlled ischaemia in patients with peripheral vascular disease. J Clin Pathol 2002;55(12):946-50.

88. Payne DA, Jones CI, Hayes PD, et al. Beneficial effects of clopidogrel combined with aspirin in reducing cerebral emboli in patients undergoing carotid endarterectomy. Circulation 2004;109(12):1476-81.

89. Pekdemir H, Cin VG, Camsari A, et al. A comparison of 1-month and 6-month clopidogrel therapy on clinical and angiographic outcome after stent implantation. Heart Vessels 2003;18(3):123-9.

90. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation 2003;108(14):1682-7.

91. Ringleb PA, Bhatt DL, Hirsch AT, et al. Benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events. Stroke 2004 ;35(2):528-32.

92. Rosendaal FR, Algra A. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1997;150(1):85, 87.

93. Rothwell PM. Lessons from MATCH for future randomised trials in secondary prevention of stroke. Lancet 2004;364(9431):305-7.

94. Sabatine, M. S.; Cannon, C. P.; Gibson, C. M.; Lopez-Sendon, J. L.; Montalescot, G.; Theroux, P.; Claeys, M. J.; Cools, F.; Hill, K. A.; Skene, A. M.; McCabe, C. H., and Braunwald, E. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med. 2005 Mar 24; 352(12):1179-89.

95. Saw J, Topol EJ, Steinhubl SR, et al. Comparison of long-term usefulness of clopidogrel therapy after the first percutaneous coronary intervention or coronary artery bypass grafting versus that after the second or repeat intervention. Am J Cardiol 2004;94(5):623-5.

96. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334(17):1084-9.

97. Schuhlen H, Hadamitzky M, Walter H, et al. Major benefit from antiplatelet therapy for patients at high risk for adverse cardiac events after coronary Palmaz-Schatz stent placement: analysis of a prospective risk stratification protocol in the Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial. Circulation 1997;95(8):2015-21.

98. Schuhlen H, Kastrati A, Pache J, et al. Sustained benefit over four years from an initial combined antiplatelet regimen after coronary stent placement in the ISAR trial. Intracoronary Stenting and Antithrombotic Regimen. Am J Cardiol 2001;87(4):397-400.

99. Schulman SP. Antiplatelet therapy in non-ST-segment elevation acute coronary syndromes. JAMA 2004;292(15):1875-82.

100. Scrutinio D, Cimminiello C, Marubini E, et al. Ticlopidine versus aspirin after myocardial infarction (STAMI) trial. J Am Coll Cardiol 2001;37(5):1259-65.

101. Shlansky-Goldberg R. Platelet aggregation inhibitors for use in peripheral vascular interventions: what can we learn from the experience in the coronary arteries? J Vasc Interv Radiol 2002;13(3):229-46.

102. Siegel AM, Sandor P, Kollias SS, et al. Transient ischemic attacks after dipyridamole-aspirin therapy. J Neurol 2000;247(10):807-8.

103. Sivenius J, Cunha L, Diener HC, et al. Second European Stroke Prevention Study: antiplatelet therapy is effective regardless of age. ESPS2 Working Group. Acta Neurol Scand 1999;99(1):54-60.

104. Sivenius J, Riekkinen PJ Sr, Laakso M. Antiplatelet treatment in elderly people with transient ischaemic attacks or ischaemic strokes. BMJ 1995;310(6971):25-6.

105. Steinhubl SR, Ellis SG, Wolski K, et al. Ticlopidine pretreatment before coronary stenting is associated with sustained decrease in adverse cardiac events: data from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) Trial. Circulation 2001;103(10):1403-9.

106. Steinhubl SR, Tan WA, Foody JM, et al. Incidence and clinical course of thrombotic thrombocytopenic purpura due to ticlopidine following coronary stenting. EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. JAMA 1999;281(9):806-10.

107. Steinhubl SR, Topol EJ. Clopidogrel with aspirin is the optimal antiplatelet regimen for intracoronary stenting. J Thromb Thrombolysis 1999;7(3):227-31.

108. Tanabe Y, Ito E, Nakagawa I, et al. Effect of cilostazol on restenosis after coronary angioplasty and stenting in comparison to conventional coronary artery stenting with ticlopidine. Int J Cardiol 2001;78(3):285-91.

109. Tijssen JG. Low-dose and high-dose acetylsalicylic acid, with and without dipyridamole: a review of clinical trial results. Neurology 1998;51(3 Suppl 3):S15-6.

110. Tsai HM, Rice L, Sarode R, et al. Antibody inhibitors to von Willebrand factor metalloproteinase and increased binding of von Willebrand factor to platelets in ticlopidine-associated thrombotic thrombocytopenic purpura. Ann Intern Med 2000;132(10):794-9.

111. Tsuruta M, Utsunomiya T, Yoshida K, et al. Effect of ticlopidine on exercise-induced platelet aggregation and exercise tolerance time in patients with ischemic heart disease. J Cardiovasc Pharmacol 1999;33(4):659-64.

112. Urban P, Macaya C, Rupprecht HJ, et al. Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: the multicenter aspirin and ticlopidine trial after intracoronary stenting (MATTIS). Circulation 1998;98 (20):2126-32.

113. van der Heijden DJ, Westendorp IC, Riezebos RK, et al. Lack of efficacy of clopidogrel pre-treatment in the prevention of myocardial damage after elective stent implantation. J Am Coll Cardiol 2004;44(1):20-4.

114. van der Meer J, Brutel de la Riviere A, van Gilst WH, et al. Effects of low dose aspirin (50 mg/day), low dose aspirin plus dipyridamole, and oral anticoagulant agents after internal mammary artery bypass grafting: patency and clinical outcome at 1 year. CABADAS Research Group of the Interuniversity Cardiology Institute of The Netherlands. Prevention of Coronary Artery Bypass Graft Occlusion by Aspirin, Dipyridamole and Acenocoumarol/Phenprocoumon Study. J Am Coll Cardiol 1994;24(5):1181-8.

115. Wienbergen H, Gitt AK, Schiele R, et al. Different treatments and outcomes of consecutive patients with non-ST-elevation myocardial infarction depending on initial electrocardiographic changes (results of the Acute Coronary Syndromes. Am J Cardiol 2004;93(12):1543-6.

116. Wong NN. Aggrenox: an aspirin and extended-release dipyridamole combination. Heart Dis 2001;3(5):340-6.

117. Yip HK, Chang HW, Wu CJ, et al. A safe and effective regimen without heparin therapy after successful primary coronary stenting in patients with acute myocardial infarction. Jpn Heart J 2000;41 (6):697-711.

118. Yoon Y, Shim WH, Lee DH, et al. Usefulness of cilostazol versus ticlopidine in coronary artery stenting. Am J Cardiol 1999;84(12):1375-80.

119. Yusuf S, Mehta SR, Zhao F, et al. Early and late effects of clopidogrel in patients with acute coronary syndromes. Circulation 2003;107(7):966-72.

120. Zachry WM, Wilson JP, Lawson KA, et al. Procedure costs and outcomes associated with pharmacologic management of peripheral arterial disease in the Department of Defense. Clin Ther 1999;21(8):1358-69.

121. Zakarija A, Bandarenko N, Pandey DK, et al. Clopidogrel-associated TTP: an update of pharmacovigilance efforts conducted by independent researchers, pharmaceutical suppliers, and the Food and Drug Administration. Stroke 2004;35(2):533-7.

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.

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period
Mueller C et al., 2003 (27), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	RCT, unblinded, multicenter	Consecutive pts. with successful stent implantation	T 250mg bid vs. C 75mg/day x 4 wks. The first dose of T (500mg) or C (75mg) was given immediately after stent implantation. All pts. received 100mg ASA daily	None
Atmaca et al., 2002 (25), Ankara, Turkey (fair)	DB, prospecitive randomized study	Consecutive pts. from March 1998 to January 2001 undergoing elective single vessel PTCA with stenting. Pt with Canadian Cardiac society Class-II stable angina pectoris and de novo lesions in large native coronary arteries.	C 300mg loading dose (LD) and then 75mg per day thereafter vs T 2 x 250mg daily. Both started on the same day as stent placement. All pts received 300mg ASA daily concomitantly	None

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(6) Allowed other medications/ interventions	(7) Method of Outcome Assessment and Timing of Assessment
Mueller C et al., 2003 (27), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	ASA 100mg every day for life. 86% on statins, Glycoprotein 2B/3A antagonist C 11%, T 7%, p 0.07	Scheduled f/u visits at 6 mos and whenever clinically indicated thereafter. All pts were contacted by questionnaire to assess vital and functional status as well as major adverse cardiac events 2 yrs after enrollment of the last patient. If pts did not return a signed questionnaire or any uncertainties remained, a MD interviewed the patients and their family MD over the phone. All information derived from contingent hospital re-admission records or provided by the referring MD or by the output. clinic was reviewed. Definition of Outcome: Primary- CV death (any death for which there was no clearly documented non-cardiac cause. Secondary- composite of cardiac death and MI (typical CP at rest followed by an increase in CK and CK-MB 2XULN and 5X ULN after CABG OR new Q waves in the ECG.
Atmaca et al., 2002 (25), Ankara, Turkey (fair)	ASA 300mg daily. Study stated that all pts were on the standard treatment of stable angina but exact therapy not listed	Coronary angiography made by Judkins technique from right femoral artery, Coronary lesions were assessed by multiple orthogonal views with coronary angiography and visually evaluated for morphologic features similar to those reported by the ACC/AHA. Ballon angioplasty and stent implantaiton was performed by 3 different invasive cardiologists. 12 lead ECG just before and immediately after coronary stenting for exclusion of an acute ischemia. A significant ST-segment depression was defined as horizontal/down sloping depression of ST segment >0.1 mV and 0.08 s after the J point that persisted more than 1 min., blood sampling for cTnT--drawn from an antecubital vein just before and 12 h after the procedure andput in a heparinzed collection vial. --measure by "Cardiac T Quantitative" equipment (Boehriner Mannheim, Germany and evaluated within 20min by "Cardiac Reader". clinical f/u during the hospital stay with respect to procedure related MMI and major clinical events. Pts were observed during hospitalization period. Definition of primary end point was the procedure-related MMI (minor myocardial injury) assessed by cardiac troponin T (cTnT) at 12 h after procedure. Secondary end-point was major clinical events (death, AMI and repeat revascularization via either by-pass surgery or PTCA.)- followed during hospital stay as well as major or minor bleeding (not defined). Deaths = cardiac origin if associated with CHF, AMI or sudden cardiac death (<1 hr after symptom onset). AMI= new Q wave or the evaluation of a current injury (ST elevation) lasting >1 day and the development of a T wave change; new specific ST elevation or depression ≥1 mV and increase in serum CK, CK-MB activity.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized
Mueller C et al., 2003 (27), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	C (65 ± 11); T (64±10) ; C 27% female and 73% male, T 26% female and 74% male; ethnicity not reported	smokers: C 28%, T: 32%, p=0.32; Previous CABG: C 15%, T: 12%, p=0.25; Previous AMI: C 48%, T: 44%, p=0.29; Unstable angina: C 40%. T: 38%; p=0.59	Number screened NR/ number eligible NR/- see Muller original paper/700 enrolled and randomized
Atmaca et al., 2002 (25), Ankara, Turkey (fair)	C group: age: 63.1 ± 8.2, 60% male, 40% female, T group: 62.1±7.4; 64% male and 46% female. All NS. Ethnicity not reported	Smokers: C group 45.7%, T group 43%, p=NS; DM C 21.6%, T 15%,p= NS; Hyperlipidemia: C group 28.9%, T group 25.4%, p=NS. Family hx for CAD: C group 30.1%, T group 26.6%, p=NS	Number screened not reported but assume it is 168 (consecutive pts); Number eligible168/number enrolled 168/158 randomized

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(11) Number withdrawn/ lost to fu/analyzed	(12a) Results
Mueller C et al., 2003 (27), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	none	**Ticlopidine + Aspirin vs Clopidogrel + Aspirin** *Outcomes at 28 and 27 months* Cardiovascular mortality: 2.3% (8/345) vs 7.3% (26/355) RR = 0.32 (0.15, 0.69); NNT = 20 (12, 54) Cardiovascular death or non-fatal MI: 5.5% (19/345) vs 11.3% (40/355) RR = 0.73 (0.46, 1.14) Nonfatal MI: 3.5% (12/345) vs 4.8% (17/355) RR = 0.73 (0.35, 1.50) Death from all causes: 2.6% (9/345) vs 8.2% (29/355) RR = 0.32 (0.15, 0.66); NNT = 18 (11, 44)
Atmaca et al., 2002 (25), Ankara, Turkey (fair)	10	**No outcome data reported.**

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Mueller C et al., 2003 (27), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	
Atmaca et al., 2002 (25), Ankara, Turkey (fair)	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Mueller C et al., 2003 (27), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	Monitored; Elicited by investigator Reported spontaneously by patient----f/u visits at 6 mos and whenever clinically indicated thereafter. Pts were contacted by questionnaire to assess vital and functional status as well as major adverse cardiac events 2 yrs after enrollment of the last patient. If questionnaire or any uncertainties remained, a MD interviewed pts and their family MD over the phone. All information derived from contingent hospital re-admission records or provided by the referring MD or by the outpatient clinic was reviewed. CK and CK-MB and ECG (along with pt's symptoms) were done to define if a MI after CABG occurred.	no adverse events reported
Atmaca et al., 2002 (25), Ankara, Turkey (fair)	Monitored--ECG, blood sampling, clinical f/u, cTnT, angiography	Ticlopidine vs Clopidogrel Bleeding: 0.0% (0/75) vs 0.0% (0/83)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Mueller C et al., 2003 (27), Germany, Switzerland f/u-long term study of original study which was published in Circulation 2000; 101:590-3, (fair)	This was not a safety study	This is a f/u study of Circulation 2000;11:590-3.Because 2 studies (CAPRIE-Lancet 1996;348:1329-39 and Mueller et al. Circulation 2000; 101: 90-3 restricted the usage of glybproprotein 2B/3A inhibition and reported a higher incidence of TSO (thrmbotic stent ocllusion) with C at 30 days (1.4% vs. 0.6%, p= 0.13), NS, it raised some concern about long-term survival. Authors extended the f/u study of the previous study to a median of 28 months. Frequent use of statins in this study was suggested that that may have induced or exaggerated differences in antiplatelet efficacy between T or C (previous reports that C activation requires the CYP-450 3A4 system and that antiplatelet activity of C is inhibited by atorvastatn and simvastatin, which are also metabolized by the CYP-450 3A4 system.) This inhibitory effect has not been reported for T.
Atmaca et al., 2002 (25), Ankara, Turkey (fair)	0	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period
Taniuchi et al., 2001 (30), USA (fair)	RCT per protocol, Prospective, single site, open-label administration of drugs--comprised of cases from 4 operators	Btw 9/9/98 and 11/14/99, 1,367 consecutive pts with successful implantation (defined as <20% residual stenosis, with TIMI 2 or TIMI 3 flow) of an FDA-approved stent in a native coronary artery or in a CABG graft were screened.	T 500mg LD or C 300mg LD administered within 1 hr of stent implantation. Drugs were administered x 2 wks but the exact dose was not stated although it was stated that T was given BID (assume 250mg bid) and C daily dose (assume 300mg qd). All pts received 325mg AS daily.	None
Muller C et al., 2000 (26), Germany (fair)	RCT, (using prespecified randomization sequence); single site; unblinded (all endpoints were adjudicated by a clinical-events committee whose members were unaware of the pt tx assignment	Sept 98-April 99 underwent successful (<50% residual stenosis without acute complications in the catheter lab resulting in death or emergency bypass grafting) stent implantation	250mg twice a day T + 100mg ASA X 4 wks vs. 75mg C + 100mg ASA x 4 wks	None

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(6) Allowed other medications/ interventions	(7) Method of Outcome Assessment and Timing of Assessment
Taniuchi et al., 2001 (30), USA (fair)	ASA 325mg every day; 2B/3A-50.2% T group and 46.1% C group p = 0.198; Post-procedural anticoagulation was up to the discretion of the operator--not stated if they were used. The majority of stents used were Boston Scientific NIR and ACS Duet stents (71% and 11.5%, respectively)	clinical f/u, blood test, angiography performed if stent closure occurred, pt reported
Muller C et al., 2000 (26), Germany (fair)	GP 2B/3A-11 % in C vs. 7% in T; p=0.07	Clinical follow-up complete in 99.9% of the patients. Baseline angiograph and repeated to document TSO (thrombus stent occlusion). Surgery or prolonged U-guided compression and femoral artery dissection or occlusion requiring urgent Percutaneous or surgical tx was defined as a severe peripheral vascular event. For quantitative coronary angiography analysis, the CAAS II system (Pie Medical, The Netherlands) was used.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized
Taniuchi et al., 2001 (30), USA (fair)	T group:63.1 years old; 60.2% males and 39.8% females in T group; C group: 63.6 years old; 61.5% males and 38.5% females; Ethnicity not-reported	AMI (41.4% of the pts were within 1 wk of MI) accounts for high incidence of angiographically evident thrombus (20.9% overall) and cardiogenic shock were not excluded. (T 18.2% vs. C 24.3% ; p=0.009) DM -29% of the population (vs. 21-23 in Mueller study (Circ.2000) and 10-12% in CLASSICS). Also, 21% overall had previous bypass grafting (include saphenous vein graft stents; stents were placed in vein grafts in 9.5% of the total population)	Number screened not reported/ number eligible not reported although had to have successful stent implantation (i.e. screened) to be randomized/number enrolled not reported/ 1016 randomized (522 T and 494 C).
Muller C et al., 2000 (26), Germany (fair)	C group 65±11 years old, 26% female, 74% male; T group 64± 10 years, 26% female, 74% male. Ethnicity not reported	approx. 50% of the stent procedures were performed in ACS. C group: 23% DM, 15% previous CABG, 48% previous MI, 40% unstable angina. In T group: 21 % DM, 12 % previous CABG; 44% previous MI; 38% unstable angina--none SS	Number screened not reported/ number eligible not reported/793 underwent stents (enrolled); 700 randomized; clinic f/u was complete for 699

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(11) Number withdrawn/ lost to fu/analyzed	(12a) Results
Taniuchi et al., 2001 (30), USA (fair)	2 pts stopped medication without an identified clinical reason; 1 from each arm of tx. 2 T pts stopped med due to reported rash-(not confirmed by PE). Additional pts had rash but were confirmed on PE ? stopped med	**Ticlopidine vs Clopidogrel** *Outcomes at 30 days* Acute closure: 0.57% (3/522) vs 0.61% (3/494) RR = 0.95 (0.19, 4.67) Subacute thrombosis: 1.3% (7/522) vs 1.4% (7/494) RR = 0.95 (0.33, 2.68) Target vessel revascularization: 2.3% (12/522) vs 2.4% (12/494) RR = 0.95 (0.43, 2.09) 30-d closure: 1.9% (10/522) vs 2.0% (10/494) RR = 0.95 (0.40, 2.25) Cardiac death: 1.5% (8/522) vs 0.6% (3/494) RR = 2.52 (0.67, 9.46) Major adverse cardiac events: 4.6% (24/522) vs 3.9% (19/494) RR = 1.20 (0.66, 2.15)
Muller C et al., 2000 (26), Germany (fair)	Not Reported	**Ticlopidine + Aspirin vs Clopidogrel + Aspirin** *Outcomes at 30 days* Cardiac events: 1.7% (6/345) vs 3.1% (11/355) RR = 0.56 (0.21, 1.50) Cardiac death: 0.3% (1/345) vs 0.3% (1/355) RR = 1.03 (0.06, 16.39) Thrombotic stent occulsion: 0.6% (2/345) vs 2% (7/355) RR = 0.29 (0.06, 1.41) Urgent target vessel revascularization: 0.6% (2/345) vs 1.7% (6/355) RR = 0.34 (0.07, 1.69) Nonfatal MI: 1.2% (4/345) vs 2% (7/355) RR = 0.59 (0.17, 2.00)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Taniuchi et al., 2001 (30), USA (fair)	
Muller C et al., 2000 (26), Germany (fair)	Noncardiac events: 9.6% (33/345) vs 4.5% (16/355) RR = 2.12 (1.19, 3.78) Noncardiac death: 0.3% (1/345) vs 0% (0/355) RR = NC Hemorrhagic complication: 0.9% (3/345) vs 0.6% (2/355) RR = 1.54 (0.26, 9.18) Vascular complication: 1.7% (6/345) vs 2% (7/355) RR = 0.88 (0.30, 2.60) Stroke: 0% (0/345) vs 0% (0/355) RR = NC

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Taniuchi et al., 2001 (30), USA (fair)	Monitored and Reported spontaneously by patient---clinical follow-up; self-reported; surgery in one case for major access site bleeding, blood counts; probably angiography if stent closure occurred	Ticlopidine vs Clopidogrel Bleeding: 0.4% (2/522) vs 0.4% (2/494) Gastrointestinal: 0.4% (2/522) vs 0% (0/494) Neutropenia: 0.4% (2/522) vs 0% (0/494) Occurrence of thrombocytopenia: 0.6% (3/522) vs 1% (5/494) Rash: 1% (5/522) vs 0.2% (1/494)
Muller C et al., 2000 (26), Germany (fair)	Monitored and Reported spontaneously by patient-Clinical follow-up, blood test, observation, pt reporting, quantitative coronary angiography analysis, CAAS II system was used	Ticlopidine + Aspirin vs Clopidogrel + Aspirin Hemorrhagic complications: 0.9% (3/345) vs 0.6% (2/355) Neutropenia or thrombocytopenia: 0.9% (3/345) vs 0% (0/355) Vascular surgical complications: 1.7% (6/345) vs 2% (7/355)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Taniuchi et al., 2001 (30), USA (fair)		Occurrence of both acute closure (within 24 hrs of implantation) and subacute stent thrombosis (day 1-30) were essentially equal for the 2 tx arms. 30 d rate of stent closure 1.92% for T and 2.02% for C are similar to the 2.0% rate reported by Muller (2000). and sl higher than the range of 0.9% T to 1.5% for C in CLASSICS. (possibly due to higher risk pts enrolled in this study-AMI, cardiogenic shock, lesions with thrombus and cases in which multiple stents were placed). 30 d rate of Major adverse stents was 4.23% overall...between Muller and CLASSICS 0.9% to 3.1%). When the occurrence of 30 d stent thrombosis of Muller, CLASSICS and TOPPS are combined, the rate associated with T is 1.16% (14/1207) and C 1.77% (24/1529) p=0.355. The combined 30 d major adverse cardiac event rate is 2.73% (33/1207) for T and 2.62 (41/1529) for C; p=8.50.
Muller C et al., 2000 (26), Germany (fair)		

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period
Leon et al., 1998 (32), USA (fair)	RCT, Multicenter; un-blinded. Also had a parallel arm registry within the study	1 or two target lesions with more than 60% stenosis in a 3-to-4 mm native coronary artery, not involving the left main coronary artery or a major coronary bifurcation. The implantation of the stent was considered successful if the final degree of stenosis within the stent was less than 10% (by visual estimate), there was no evidence of thrombus or of dissections (more than grade B according to the NHLB Institute criteria, there was grade 3 flow according to TIMI criteria, and no more than 2 stents were needed to treat one long (≤ 25 mm) lesion or two focal (≤ 12 mm) lesions in 1 or two native coronary arteries. If successful, then pt was eligible to be randomized.	All pts received nongeneric, non-enteric coated ASA 325mg and IV heparin (10,000-15,000 U) to maintain an activated clotting time of 250-300 s during stents prior to randomization. 3 antithrombotic drug regimens used: ASA 325mg/day (non-enteric) x 4 wks; 325 mg of non-enteric ASA+ IV heparin to achieve APTT of 40-60 s and DC once an INR of 2-2.5 s was reached with oral warfarin x 4 wks; and 325mg non-enteric/day and 250mg T bid x 4 wks. First dose of T or warfarin was administered at the conclusion of the stenting procedure.	Pts who did not meet the criteria for successful stenting were enrolled in a prospective trial that was identical to the randomized trial in terms of data collection and f/u except pts were not assigned to a specific drug-tx strategy
Bertrand et al., 2000 (29), USA, CLASSICS (good)	RCT, DB, Multicenter, parallel-group	Successful planned or unplanned coronary stenting (1 or 2 stents) in a single vessel (reference vessel diameter >2.8 mm) with the use of any commercially available non-heparin-coated stents; <10% adjacent residual stenosis; no angiographic evidence of thrombus formation or dissection within the treated vessel; blood flow of TIMI grade 3 in each stented segment and associated major side branches; preoperative CPK less than 2x ULN; and eligibility to commence study drug within 6 hours after stent implantation	Initiated within 6 hrs of completion of stenting. 1. 300mg C (LD) and 325mg/day ASA on day 1, followed by 75mg daily C and 325 mg/day ASA (days 2-28) 2. 75mg/day C and 325mg/day ASA (days 1-28); 3. 250mg twice a day T and 325mg/day ASA (days 1-28). (ASA was given in a blinded fashion in all arms)	None

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(6) Allowed other medications/ interventions	(7) Method of Outcome Assessment and Timing of Assessment
Leon et al., 1998 (32), USA (fair)	Not reported	Detailed case-report forms completed by clinical coordinator at each site; monitored by independent study monitors and submitted to the data-coordinating centers. Angiograms, assessed for AE at discharge and then 4 wks post stenting. All events were classified by an independent clinical events committee whose members were unaware of the pts' tx assignments.
Bertrand et al., 2000 (29), USA, CLASSICS (good)	See Exclusion Criteria	A Critical Event Adjudication Committee validated all potential outcome events --only validated events were analyzed. The primary end point was the incidence of any one of the following validated events occurring during the study drug treatment period between visits 1 and 4 or until discontinuation of study drug 1. major peripheral or bleeding complications(including false aneurysms, surgical repair of puncture site complications, blood transfusion (≥2 U of blood), intracranial bleeding, retroperitoneal bleeding, overt hemorrhage with a decrease of Hgb ≥ 3 g/dL compared with BL) 2. neutropenia -(< 1.5 x 109/L) 3. thrombocytopenia-plt < 100 x 109/L 4. early discontinuation of study drug because of noncardiac adverse event (including death of noncardiac origin)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized
Leon et al., 1998 (32), USA (fair)	ASA alone: 61±11 years old; 28% female and 72% male; ASA and warfarin: 62 years old ±11; 30% female and 70% male; ASA and T 61±12 years old, 29% female and 71% male. Ethnicity not reported	DM (18, 20, 18%); Smoking (27,29, 29%), single-vessel disease (67,67,68%); Previous MI (32,39,36%) in the ASA, ASA + warfarin and ASA and T groups respectively. Not all data were available for all the pts for previous restenosis, lesion grade B2 or C, ostial location of lesion, bifurication or target vessel LAD	1965 pts with 2147 lesions were enrolled (screened) between 2/96 and 11/96.1653pts with 1772 lesions eligible and were randomized. The remaining 312 pts with 375 lesion s were enrolled in a parallel registry.
Bertrand et al., 2000 (29), USA, CLASSICS (good)	T group 61 ± 9.9 years old; 75% male and 25% female; C group (without LD) 60 ± 10.4 years old; 78% male and 22% female; C group with LD: 60 ± 10.1 years old; 77% male and 23% female. Ethnicity not stated.	Overall: HTN 49.9%; DM (11.3%); former or current smoker 69%, tx for hypercholesterolemia (57%);previous stable angina (55.8%)	Number of patients screened not reported/number eligible not reported/1021 enrolled/1020 randomized

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(11) Number withdrawn/ lost to fu/analyzed	(12a) Results
Leon et al., 1998 (32), USA (fair)	0	**Ticlopidine + Aspirin vs Aspirin** *Outcomes at 30 days* Death: 0% (0/546) vs 0.2% (1/557) RR = NC Revascularization of target lesion: 0.5% (3/546) vs 3.4% (19/557) RR = 0.05 (0.01, 0.39); NNT = 30 (21, 60) Angiographically evident thrombosis: 0.5% (3/546) vs 2.9% (16/557) RR = 0.19 (0.06, 0.65); NNT = 43 (26, 124) Recurrent MI: 0.5% (3/546) vs 2.7% (15/557) RR = 0.20 (0.59, 0.70); NNT = 47 (28, 151)
Bertrand et al., 2000 (29), USA, CLASSICS (good)	1	**Ticlopidine vs Clopidogrel 75mg vs Clopidogrel 300/75mg** *Outcomes at 28 days* (*All RRs based on T vs C75mg) MI: 0.3% (1/340) vs 0.3% (1/335) vs 0.6% (2/345) RR = 0.99 (0.06, 15.69) MI + Target lesion revascularization: 0.3% (1/340) vs 0.9% (3/335) vs 0% (0/345) RR = 0.33 (0.03, 3.14)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Leon et al., 1998 (32), USA (fair)	
Bertrand et al., 2000 (29), USA, CLASSICS (good)	Fatal MI: 0% (0/340) vs 0% (0/335) vs 0.3% (1/345) RR = NC Sudden death: 0% (0/340) vs 0% (0/335) vs 0.3% (1/345) RR = NC Target lesion revascularization: 0.3% (1/340) vs 0.3% (1/335) vs 0% (0/345) RR = 0.99 (0.06, 15.69) ≥ 1 cardiac event : 0.9% (3/340) vs 1.5% (5/335) vs 1.2% (4/345) RR = 0.59 (0.14, 2.45)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Leon et al., 1998 (32), USA (fair)	Monitored-detailed case-report by the clinical coordinator at each site, monitored by independent study monitors, angiograms were submitted to the angiographic core lab and analyzed with a computer-based system. pts assess at discard and 4 wks after stenting. All events were classified by an independent clinical events committee, blood tests, EC, procedure-related bleeding episode requiring transfusion	Ticlopidine + Aspirin vs Aspirin Cerebrovascular: 0.0% (0/546) vs 0.4% (2/557) Hemorrhagic complications: 5.5% (30/546) vs 1.8% (10/557) Neutropenia or thrombocytopenia: 0.5% (3/546) vs0.2% (1/557) Vascular surgical complications: 2.0% (11/546) vs 4.0% (2/557)
Bertrand et al., 2000 (29), USA, CLASSICS (good)	Monitored at weekly visits	Ticlopidine vs Clopidogrel 75mg vs Clopidogrel 300/75mg Allergy: 1.2**%** (4/340) vs 0.00% (0/335) vs 0.00% (0/345) Gastrointestinal disorder: 2.6% (9/340) vs 2.4% (8/335) vs 0.3% (1/345) Major peripheral or bleeding complication: 1.2% (4/340) vs 1.2% (4/335) vs 1.5% (5/345) Neutropenia <1.5 x 10to9/L: 0.3% (1/340) vs 0.00% (0/335) vs 0.00% (0/345) Skin disorder: 2.6% (9/340) vs 0.9% (3/335) vs 0.6% (2/345) Thrombocytopenia 70-100x10to0/L: 0.3% (1/340) vs 0.00% (0/335) vs 0.00% (0/345)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Leon et al., 1998 (32), USA (fair)		No significant difference in the risk of neutropenia or thrombocytopenia btw the groups
Bertrand et al., 2000 (29), USA, CLASSICS (good)	T: 28, C: 17, C (LD): 7	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period
Hall, 1996 (28), Japan, Italy (poor)	randomized, single-center conducted between Jan 1994 and Mar. 1995. parallel univariate risk analysis of the CAPRIE trial	Coronary artery disease manifested by clinical symptoms or objective evidence of MI either on exercise test or by nuclear scintigraphy and angiographic evidence of single-vessel or multivessel coronary disease with target lesion stensosis >70% by visual estimate. The study required completion of a successful intravascular US guided stent implantation procedure--included qualitative evaluation of the stent site involving the achievement of good stent appostion to the vessel wall with good plaque compression. The quantitative criterion for stent expansion used was the achievement of an intrastent lumen CSA (at the tightest measured point) that was 80% of the distal reference lumen CSA. In smaller vessels in which the lesions had a measured CSA of <7.5mm, the quantitative criterion was modified so that it was the achievement of stent lumen greater than the distal lumen CSA. 6 different types of stents used: Palmaz-Schatz (Johnson and Johnson Interventional Systems CO), Gianturco-Roubin (Cook Cardiology, Cook, Inc), Gianturco-Roubin (Cook Cariodlogy Cook), Wiktor (Medtronic, Inc), Micro (Applied Vascular Engineering) Wall (Schneider Inc), and the Cordis (Cordis Corp) stents.	T 250mg twice a day x 1 month with short-term ASA 325mg x 5 days OR ASA 325mg/day. T not administered before or during the stent procedure but only after successful procedure (intravascular US criteria for optimal stent expansion were met and the angiographic result was acceptable)	None
Diener, 2004 (11), Europe, USA (good)	DB, RCT, centers (stroke units and neurology departments) in 28 countries (507 centers). Study conducted between Dec. 2000 and Apr. 2002.	ischemic stroke or TIA in the previous 3 months and had one or more 5 additional risk factors- previous ischemic stroke, previous MI, angina pectoris, DM or symptomatic PAD-within the previous 3 years.	ASA 75mg per day + clopidogrel 75mg daily vs. placebo and clopidogrel 75mg daily x 18 months. (patients were already taking clopidogrel prior to entering into the study)	None

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(6) Allowed other medications/ interventions	(7) Method of Outcome Assessment and Timing of Assessment
Hall, 1996 (28), Japan, Italy (poor)	intracornary NTG before baseline and final angiograms. Pts received ASA 325mg and calcium channel antagonists before stent deployment. A bolus of 10000 U heparin was given after sheath insertion with an additional bolus of 5000U given as needed to maintain the activated clotted time to >250 seconds.	Clinical f/u was performed by telephone contact of all pts within 1-4 mos of hospital discharge. Short term complications (stent thrombosis) were assessed continually through regular and uniform contact of all pts within 4 wks of hospital discharge and 2 mos later. Comparison of clinical events and medication side effects within the first month after a successful stent procedure was performed. Angiographic data were obtained for all lesions at 1 month and quantitative intravascular US measurements performed for all lesions. Coronary angiograms were analyzed without knowledge of the intravascular ultrasound data by experienced angiographers not involved in the stenting procedure. a central validation committee was blinded to tx assignment adjudicated all outcomes
Diener, 2004 (11), Europe, USA (good)	80% of pts were receiving ASA	f/u visits were scheduled at 1,3,6,12,and 18 months. Visits were supplemented by monthly follow-up telephone calls to pts.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized
Hall, 1996 (28), Japan, Italy (poor)	ASA group 58 years old ±10; 89% male and 11% female. T + ASA group 57 years old ± 9; 88% male and 12% female. Ethnicity not reported	Previous MI in the ASA vs. T + ASA group -48% and 50% respectively. 10% in both groups had had an angioplasty before. % of CABG in each group-already reported. In the ASA group 39% currently smoking vs. 29% in the T + ASA group-p= NS. 40% in both groups had HTN p = .01. 6% DM in ASA group vs. 16% in the T + ASA group ; p=0.9. Unstable angina- 28% in ASA group vs. 33% in T + ASA group p=0.5	Number screened not reported/number eligible not reported/number enrolled not reported although stated stent deployment attempted in 358/226 randomized
Diener, 2004 (11), Europe, USA (good)	ASA + C group: 66.5 years old ± 9.9; 37% women and 63% men. Placebo + C group: 66.1 years old ± 9.9; 37% women and 63% men Ethnicity not reported	27% (ASA + C) vs. 26% (P + C) previous ischemic stroke before qualifying event; 5% in both group previous MI; 10% in each group with PAD, 68% in both groups with DM, 48 and 47% past or current smoker. The most prevalent risk factor at randomization were HTN (78%); DM (68%); and hypercholesterolemia (56%). 26% had previous ischemic stroke and 19% had TIA. Most patients (79%) had one additional risk factor and 20% had two or more. Most pts had lacunar strokes due to microangiopathy, which might not be of pure atherothrombotic origin.	Number screened not reported/number eligible not reported/ number enrolled not reported/ 7599 randomized. At 18 months of f/u- data was available for 7276 pts (96%)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(11) Number withdrawn/ lost to fu/analyzed	(12a) Results
Hall, 1996 (28), Japan, Italy (poor)		**Ticlopidine Aspirin vs Aspirin** *Outcomes at 1 month* Stent thrombosis: 0.8% (1/123) vs 2.9% (3/103) RR = 0.28 (0.29, 2.64) MI: 0.8% (1/123) vs 3.9% (4/103) RR = 0.21 (0.02, 1.84) Emergency bypass: 0% (0/123) vs 0% (0/103) RR = NC Elective bypass: 0% (0/123) vs 0% (0/103) RR = NC Death: 0% (0/123) vs 2.9% (3/103) RR = NC Repeat PTCA: 0.8% (1/123) vs 1.9% (2/103) RR = 0.42 (0.04, 4.55) Any major event: 0.8% (1/123) vs 3.9% (4/103) RR = 0.21 (0.02, 1.90)
Diener, 2004 (11), Europe, USA (good)	4 lost to f/u- ASA + C group; 9 lost to f/u in P + C group. 270 pts in both group discontinued treatment for a reason other than endpoint or adverse event	**Clopidogrel + Aspirin vs Clopidogrel + Placebo** *Outcomes at 18 months* MI (fatal or not): 1.6% (59/3797) vs 1.6% (62/3802) RR = 0.95 (0.67, 1.36) Ischemic stroke (fatal or not): 7.9% (299/3797) vs 8.4% (319/3802) RR = 0.94 (0.81, 1.09) Other vascular death: 1.8% (69/3797) vs 1.9% (74/3802) RR = 0.93 (0.67, 1.29) Rehospitalization for acute ischemic event: 4.5% (169/3797) vs 4.8% (181/3802) RR = 0.93 (0.76, 1.15)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Hall, 1996 (28), Japan, Italy (poor)	
Diener, 2004 (11), Europe, USA (good)	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Hall, 1996 (28), Japan, Italy (poor)	Monitored	Ticlopidine + Aspirin vs Aspirin Vascular complication: 0% (0/123) vs 1% (1/103) Leukopenia: 0.8% (1/123) vs 0.0% (0/103) Skin rash: 1.6% (2/123) vs 0.0% (0/103)
Diener, 2004 (11), Europe, USA (good)	Monitored	Clopidogrel + Aspirin vs Clopidogrel + Placebo Life-threatening bleeding: 2.6% (96/3759) vs 1.3% (49/3781) Fatal-bleeding: <1.0% (16/3759) vs <1.0% (11/3781) Non-fatal bleeding: 1.0% (38/3781) vs 2.0% (81/3759) Symptomatic intracranial: 1.0% (25/3781) vs 1.0% (40/3759) Primary intracranial hemorrhage: 1.0% (32/3759) vs <1.0% (17/3781) Major bleeding: 1.9% (73/3759) vs 0.6% (22/3781)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Hall, 1996 (28), Japan, Italy (poor)		
Diener, 2004 (11), Europe, USA (good)		Ongoing trials: CHARISMA -C + ASA along in primary and secondary prevention (Cerbrovasc Dis 2004; 17(suppl 3): 11-16. FASTER pts with CV disease of different causes : acute TIA and minor ischemic stroke; SPS3-lacunar strokes in Secondary Prevention of Small Subcortical Strokes and ischemic strokes arising from aortic arch plaques in ARCH. (no references for these last trials were provided)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period
Gorelick et al., 2003 (41), USA (fair/good)	RCT, DB, multicenter between Dec. 1992 and Oct 2001 with 2 year f/u	African American race; 29-85 years of age with a noncardioembolic ischemic stroke (confirmed by cranial computed tomographic scan or magnetic resonance image of the brain consistent with occurrence of the entry cerebral infarct; measurable neurological deficit that correlates at onset with entry cerebral infarct with onset at least 7 days but not more than 90 days; pts needed to be available to be follow up in an outpatient tx program.	250mg twice a day Ticlopidine + Placebo twice a day with meals vs. 325mg ASA twice a day+ placebo twice a day with meals x 2 years	None

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(6) Allowed other medications/ interventions	(7) Method of Outcome Assessment and Timing of Assessment
Gorelick et al., 2003 (41), USA (fair/good)	At the time the blinded phase of the study was halted by the data and safety monitoring board on 7/15/02 - [recruitment and f/u had been ongoing for about 6.5 yrs] because futility analyses indicated a <1% chance of ticlopidine being significantly better than ASA therapy in the prevention of primary outcome if the trial were to continue to completion. 47.1% of the pts had not completed the 2-yr f/u period; the patients were given the option of remaining in the study taking study-sponsored open-label aspirin or transition into the community for stroke prevention therapy according to their community physician. 307 (41%) in the ticlopidine group and 403 (44.4%) in the ASA group completed the 24 month examination.	Laboratory studies: BUN, plt ct, CBC, serum Cr, lipid panel, bilirubin, ALT, AST, LDH, alkaline phosphatase; serum glucose, electrolytes, and UA. before entry, at 12 and 24 mos, and at any time a pt experienced an outcome event or terminated from the trial. CBC and plt count were performed every 2 wks during the first 3 mos of the study or at any unscheduled time the local investigative team deemed it was indicated. Study particpants were examined in person at baseline, every 2 wks during the first 3 months, and at 6, 10, 12, 16, 20 and 24 months; and at any unscheduled time the investigative team deemed it was indicated for pt safety, medication complicance, or the occurrence of outcome events or SAEs. Telephone contact was made during study months for which pts did not have an in-person exam to screen for med compliance, outcome events, and SAEs. A predetermined lab "panic value" system whereby the main lab noticied the local investigative team and the clinical safety monitor of a critical value; an internal inhouse safety committee; and an external data safety and monitoring board appointed by the NIH.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized
Gorelick et al., 2003 (41), USA (fair/good)	T group: 60.9 years old ± 10.7, 54.5% women, 45.5% male and 61.6± 10.4 years old, 52.4% female and 47.6% male in the ASA group. 100% African American	Patients in the ticlopidine group had ≤ 73.8% in Ticlopidine and 74.5% in the ASA group had high school or less education; 44% were making less than 14999 household income vs. 44.4% in ASA group. 85% had HTN vs. 86.3% in ASA group, 40% DM vs. 42.1% in ASA, 62% past/current smoking vs. 61.9% in ASA.; 40.6% in Ticlopidine group vs. 43.6% in ASA group had hypercholesterolemia.	Number screened not reported/number eligible not reported/number enrolled not reported/1809 randomized

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(11) Number withdrawn/ lost to fu/analyzed	(12a) Results
Gorelick et al., 2003 (41), USA (fair/good)	15.2% in ticlopidine treatment group and 13.3% ASA group	**Ticlopidine vs Aspirin:** *Outcomes at 2 years* Fatal recurrent stroke: 0.4% (4/902) vs 0.2% (2/907) RR = 2.01 (0.37, 10.95) Nonfatal recurrent stroke: 11.3% (102/902) vs 9.3% (84/907) RR = 1.22 (0.93, 1.61) Fatal MI: 0.1% (1/902) vs 0% (0/907) RR = NC Nonfatal MI: 0.9% (8/902) vs 0.9% (8/907) RR = 1.01 (0.38, 2.67) Major vascular death: 0.8% (7/902) vs 0.4% (4/907) RR = 1.76 (0.52, 5.99) Other vascular death: 1.2% (11/902) vs 1.5% (14/907) RR = 0.79 (0.36, 1.73) Any recurrent stroke: 11.9% (107/902) vs 9.5% (86/907) RR = 1.25 (0.96, 1.64)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Gorelick et al., 2003 (41), USA (fair/good)	All cause death: 5.0% (45/902) vs 4.4% (40/907) RR = 1.13 (0.75, 1.71) Vascular death: 2.5% (23/902) vs 2.1% (19/907) RR = 1.22 (0.67, 2.22) Recurrent stroke or All cause death: 15.3% (138/902) vs 12.9% (117/907) RR = 1.19 (0.94, 1.49) Recurrent stroke, MI or All cause death: 16.1% (145/902) vs 13.8% (125/907) RR = 1.16 (0.94, 1.45)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Gorelick et al., 2003 (41), USA (fair/good)	Monitored	Ticlopidine vs Aspirin Cardiovascular system: 7.3% (66/902) vs 8.4% (76/907) Diarrhea: 0.3% (3/902) vs 0.2% (2/907) Digestive system: 4.2% (38/902) vs 4.7% (43/907) Endocrine system: 1.2% (11/902) vs 1.1% (10/907) Hemic & lymphatic system: 4.2% (38/902) vs 3.2% (29/907) Major GI tract hemorrhage: 0.4% (4/902) vs 2.2% (20/907) Musculoskeletal system: 1.9% (17/902) vs 1.2% (11/907) Nervous system: 7.3% (66/902) vs 6.6% (60/907) Neutropenia: 3.4% (31/902) vs 0.9% (8/907) Other bleeding : 0.7% (6/902) vs 1.2% (11/907) Psychiatric system: 1.1% (10/902) vs 0.6% (5/907) Respiratory system: 4.2% (38/902) vs 4.1% (37/907) Skin & appendages: 1.7% (15/902) vs 1.7% (15/907) Special senses: 0.3% (3/902) vs 0.7% (6/907) Thrombocytopenia: 0.3% (3/902) vs 0.2% (2/907) Urogenital system: 2.7% (24/902) vs 1.9% (17/907)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Gorelick et al., 2003 (41), USA (fair/good)		

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period
CAPRIE Steering Committee, 1996 (13), International (good)	RCT, blinded; multicenter conducted btw Mar. 1992 and Feb. 1995.	dx of ischemic stroke, (including retinal and lacunar infarction) was defined as ● focal neurological deficit likely to be of atherothrombotic origin, ● Onset >1 wk and ≤6 mos before randomization, ● Neurological signs persisting ≥1 wk from stroke onset ● CT or MRI ruling out hemorrage or non-relevant disease. MI defined as ● Onset ≤35 d before randomization ●2 of the following: -characteristic ischemic pain for ≥ 20 min,-elevation of CK, CK-MB, LDH, or AST to 2x upper limit of laboratory normal with no other explanation, -developement of new ≥40 Q waves in at least two adjacent ECG leads or new dominant R wave in V1 (R≥1 mm > S in V1) or symptomatic atherosclerotic PAD defined as ●Intermittent claudication (WHO: leg pain on walking, disappearing in <10 min or standing) or presumed atherosclerotic origin; and ankle/arm systolic BP ratio ≤0.85 in either leg at rest (2 assessments on separate days); or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty with no persisting complications from intervention had to be established.	blister packs containing either 75mg of clopidogrel + ASA placebo OR 325mg ASA plus clopidogrel placebo to take with morning meal x 1-3 years (mean 1.9 years)	use of anticoagulants or antiplatelet drugs were discontinued before randomization and thrombolytic treatment should not have been received within the previous 48 hours.
Diener et al., 1996 (10), *I*nternational, ESPS-2 (good)	RCT, 2x2 factorial, DB, PC, multicenter trial at 59 sties in 13 countries between 2/89 and March 1995	older than 18 years old and had experienced a TIA (clinical neurological symptoms persisting for less than 24 h) or a completed ischemic stroke (clinical neurological deficit lasting more than 24 h) within the preceding 3 months. Diagnosis based on clinical neurological examination only was acceptable but CT or MRI were recommended to confirm the diagnosis.	ASA 50mg; dipyridamole SR (Persantine Retard) 200mg twice a day; ASA/DP, placebo x 2 years	None

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(6) Allowed other medications/ interventions	(7) Method of Outcome Assessment and Timing of Assessment
CAPRIE Steering Committee, 1996 (13), International (good)	Not reported	f/u visit was monthly for the first 4 months and every 4 mos thereafter. Information on AE, use of study drug and concomitant meds, blood for hematological and biochemical assessment made by 1 of 3 central laboratories. Compliance was assessed by counting returned tablets. Human safety data on clopidogrel--weekly assessment of blood counts and 2-wkly assessments of biochemistry during the first 3 mos. After 500 pts were entered, a blinded review of these data by steering committee did not show any cause for concern, so the frequency of these assessment was halved. Alert values of <1.2 x 10 9/L for neutrophils and <100x 109/L for platelets were established whereby investigators were to begin daily complete blood counts. If cts < 0.45 x 10 9/L or 80 x 10 9/L for neutrophils and platelets respectively the study drug was to be permanently DCs.
Diener et al., 1996 (10), International, ESPS-2 (good)	Not reported	General medical examination was performed and included BP measurement and electrocardiogram.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized
CAPRIE Steering Committee, 1996 (13), International (good)	mean age 62.5 ± 11.1 in the clopidogrel and 62.5 ± 11.1 in the ASA group. Both groups had 72 % male, 28% female and 95% white.	20% DM, 52% HTN, 22% stable angina, 9% unstable angina, 17% MI (not including the qualifying event), 29% current smokers, 49% ex smokers in both groups	Number screened not reported/ number eligible not reported/ number enrolled/not reported/19185 randomized
Diener et al., 1996 (10), International, ESPS-2 (good)	Mean age: Placebo: 66.6, ASA: 66.8, DP: 66.7, DP-ASA: 66.8 Sex M/F: Placebo: 57.7%/42.3%; ASA 58%/42%; DP 58.3%/41.7%; DP-ASA; 57.9%/42.1%	Diabetes: placebo 14.5%; ASA 14.6%; DP 16.8%; DP-ASA 15.4% HTN: placebo 62%; ASA 59.6%; DP 61.2%; DP-ASA 59.4% Current Smoker: placebo 23.5%; ASA 23.5%; DP 23.9%; DP-ASA 25.6% PVD: placebo 22%; ASA 22%; DP 22.4%;DP-ASA 21.7%	#screened-not reported, # eligible-unknown; 7054 enrolled and randomized; 6602 pts analyzed (438 pts omitted- 1 center excluded due to serious inconsistencies). Statistical analyses were performed for the original 7054 data base as well as the 6,602 patient data base.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(11) Number withdrawn/ lost to fu/analyzed	(12a) Results
CAPRIE Steering Committee, 1996 (13), International (good)	42 (0.22%) were lost to f/u-22 in the clopidogrel and 20 in the ASA group. 21.2% had study drug permanently discontinued early for reasons other than the occurrence of an outcome event; 21.3% in the clopidogrel and 21.1% in the ASA group. 46 pts did not receive clopidogrel as allocated vs. 40 in the ASA group although they were included in the analysis	**Clopidogrel vs Aspirin** *Outcomes at 36 months* Ischaemic stroke, MI, or vascular death: 9.8% (939/9553) vs 10.7% (1021/9546) RR = 0.92 (0.84, 1.00) Ischaemic stroke, MI, amputation, or vascular death: 10.2% (979/9553) vs 11.0% (1051/9546) RR = 0.93 (0.86, 1.01) Vascular death: 3.7% (350/9553) vs 4.0% (378/9546) RR = 0.93 (0.80, 1.07) Any stroke, MI or death from any cause: 11.9% (1133/9553) vs 12.6% (1207/9546) RR = 0.94 (0.87, 1.01) Death from any cause: 5.9% (560/9553) vs 6.0% (571/9546) RR = 0.98 (0.88, 1.10)
Diener et al., 1996 (10), International, ESPS-2 (good)	see above	**Dipyridamole vs Dipyridamole + Aspirin vs Aspirin vs Placebo** *Outcomes at 24 months* (RR based on D+A vs A) Death: 11.4% (188/1654) vs 11.2% (185/1650) vs 11.0% (182/1649) vs 12.2% (202/1649) RR = 1.02 (0.84, 1.23)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
CAPRIE Steering Committee, 1996 (13), International (good)	
Diener et al., 1996 (10), International, ESPS-2 (good)	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
CAPRIE Steering Committee, 1996 (13), International (good)	Monitored	Clopidogrel vs Aspirin Abnormal liver function: 3.0% (285/9599) vs 3.2% (302/9586) Any bleeding disorder: 9.3% (890/9599) vs 9.3% (890/9586) Diarrhea: 4.5% (428/9599) vs 3.4% (322/9586) GI haemorrhage: 2.0% (191/9599) vs 2.7% (255/9586) Indigestion/nausea/vomiting: 15.0% (1441/9599) vs 17.6% (1686/9586) Intracranial haemorrhage: 0.4% (34/9599) vs 0.5% (47/9586) Rash: 6.0% (578/9599) vs 4.6% (442/9586)
Diener et al., 1996 (10), International, ESPS-2 (good)	Monitored	same adverse events as 268

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
CAPRIE Steering Committee, 1996 (13), International (good)		The plans were to recruit 15000 pts, 5000 in each of the clinical subgroups, over 3 years and to terminate the study after 1 further year of follow-up. If the recruitment over time was uniform, this sample would have resulted in a mean duration of potential f/u of 2.33 years/pt and 35000 pt/years at risk. Assumed expected 3 year event rates would be 25% for the primary outcome cluster for pts entering the study with recent stroke or MI and 14% for pts entering with PAD. Study expected to have 90% power to detect an overall relative-risk reduction of 11.6%. The expected width of the corresponding 95% CI would be about 8%. Pt recruitment was achieved well ahead of schedule and 15000 had been randomised after only 2 years and 3 months. A blinded review of overall outcome event rates showed them to be lower than initial expectation. So, pt recrutment was continued but staggered closing dates and hence, completion dates, 1 year later: PAD would finish 2 months before pts with MI who would finish 2 months before pts with stroke.Revised estimate of RRR would be 12-13%.
Diener et al., 1996 (10), International, ESPS-2 (good)		Prior to unblinding of the data, the data quality control unit identified 2 issues that required investigation: 1. 14 randomization numbers were issued that did not correspond to existing pts 2. Serious inconsistencies in pt case record from and compliance assay determinations led the Steering Committee to question the reliability of data from one centre which had randomized 438 pts. total. The data from this centre were excluded before unblinding the data. The results presented are based on 6,602 pts and not the total 7054.On the side note, the excluded patients had no impact on the results reported in this paper.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period
ESPS-2 authors, 1997(38), International, ESPS-2 (good)	Randomized, 59 clinical centers in 13 European between 2/89 and 3/95	All pts had experienced a recent (within the preceding 3 months) ischemic CVA episode as a qualifying event	Placebo, ASA 50mg; modified release dipyridamole 400mg used alone or in combination x 2 years	None
Juergens et al., 2004 (23), Australia (poor)	RCT, not blinded	Intracoronary stents were successfully deployed (<30% residual stenosis without acute complications in the catheterization laboratory resulting in death or emergency bypass surgery) from July 1999 until January 2001.	ticlopidine 500mg (LD) immediately after procedure and then 250mg twice a day+ ASA or clopidogrel 150mg (LD) immediately after procedure and then 75mg every day+ ASA x 14 days. All pts received >=300mg ASA in the 24 hrs before the procedure and a minimum of 100mg/day for duration of the study	None

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(6) Allowed other medications/ interventions	(7) Method of Outcome Assessment and Timing of Assessment
ESPS-2 authors, 1997(38), International, ESPS-2 (good)	Not reported	Patient reporting; all adverse events were recorded by the investigator at each follow-up visit. Patient compliance--measurement of plasma salicylic acid (SA) and DP concentrations in randomly selected pt (15%); pt questioning as to taking the prescribed drug regularly; counting of residual capsules in the packages used by the pt. laboratory: leucocytes, erythrocytes, plt, HCT, HG, SR, BUN, Cr, Uric acid, FBS, TC, LDL and fibrinogen were measure at entry, after 12 months and 24 months.
Juergens et al., 2004 (23), Australia (poor)	Heparin was administered as boluses to maintain an activated clotting time > 250 seconds, and GP 2B/3A could be used at the operator's discretion and in fact was used in 23% of the pts receiving ticlopidine and 25% of pts in the clopidogrel group. Heparin could be restarted after sheath removal at the operator's discretion.	30 day MACE, clinical f/u

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized
ESPS-2 authors, 1997(38), International, ESPS-2 (good)	< 60 years and male with TIA -322 pts; < 60, years and female with TIA- 169 pts; (Total TIA pt = 1562) < 60 years and female with stroke 327 pts; ≥ 60 years and male with TIA- 554 pts; (Total # stroke pts- 5038) ≥ 60 years and female with TIA- 517 pts. Ethnicity not reported. Report does provide breakdown of those between 50-59, 60-69 and 70-79.	76.3% had stroke and 23.7% had TIA as ischemic CVA episode as the qualifying events. Article provides breakdown of # of pts with multiple other conditions	# screened/eligible not reported. 7054 were randomized. 6602 pts data were analyzed for final report
Juergens et al., 2004 (23), Australia (poor)	Ticlopidine group: mean age 60 ± 10; male%/female% 80/20. In clopidogrel group: mean age 60± 12; male% female% 71/29. Ethnicity not reported	T group: 58% HTN, 23% DM, 17% current smoker, 72% hypercholesterolemia, 12% Previous CABG, 10% recent MI, 47% unstable angina. Clopidogrel group: 56% HTN, 19% DM, 21% current smoker, 79% hypercholesterolemia, 7% previous CABG, 14% recent MI and 44% Unstable angina	Number of pts screened not reported/number eligible not reported/number/enrolled and randomized 307

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(11) Number withdrawn/ lost to fu/analyzed	(12a) Results
ESPS-2 authors, 1997(38), International, ESPS-2 (good)	138 cases (2.1%) were either misdiagnosed or not included into the study--4 tx groups each contained approx 1/4 of these pts, so that misdiagnosis or not included is not expected to change significantly the results in the intention-to-treat analysis. Loss to f/u-42 pt (0.6%) of trial population. These subjects were also equally distributed over the 4 treatment groups. 1/4 of all pts stopped treatment for a reason (medical or non-medical) other than reaching an endpoint. Tx cessations were 7.2% more frequent in the 2 DP groups 29.2% than in the non-DP groups (22.0%).	**Dipyridamole vs Dipyridamole + Aspirin vs Aspirin vs Placebo** (All RRs based on D+A vs A) *Outcomes at 24 months* All strokes: 12.8% (211/1654) vs 9.5% (157/1650) vs 12.5% (206/1649) vs 15.2% (250/1649) RR = 0.76 (0.63, 0.93); NNT = 34 (20, 118) Non-fatal strokes: 11.1% (183/1654) vs 8.3% (137/1650) vs 11.3% (186/1649) vs 13.8% (228/1649) RR = 0.74 (0.60, 0.91); NNT = 32 (19, 90)
Juergens et al., 2004 (23), Australia (poor)	0	**Ticlopidine + Aspirin vs Clopidogrel + Aspirin** *Outcomes at 30 days* Cardiovascular death: 0.7% (1/153) vs 0% (0/154) RR = NC Non-fatal MI: 1.3% (2/153) vs 1.3% (2/154) RR = 1.0 (0.14, 7.00) Urgent target vessel revascularization: 0.7% (1/153) vs 1.9% (3/154) RR = 0.34 (0.04, 3.19) MACE: 2.0% (3/153) vs 1.9% (3/154) RR = 1.0 (0.21, 4.91) Thrombotic stent occlusion: 0.7% (1/153) vs 1.9% (3/154) RR = 0.34 (0.04, 3.19)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
ESPS-2 authors, 1997(38), International, ESPS-2 (good)	Fatal strokes: 3.4% (56/1654) vs 2.3% (38/1650) vs 2.4% (39/1649) vs 2.6% (43/1649) RR = 0.97 (0.63, 1.51) At least one TIA: 13.0% (215/1654) vs 10.4% (172/1650) vs 12.5% (206/1649) vs 16.2% (267/1649) RR = 0.83 (0.69, 1.00) Stroke or TIA: 23.1% (382/1654) vs 18.1% (299/1650) vs 22.6% (372/1649) vs 28.7% (473/1649) RR = 0.80 (0.70, 0.92); NNT = 23 (14, 59) MI: 2.9% (48/1654) vs 2.1% (35/1650) vs 2.4% (39/1649) vs 2.7% (45/1649) RR = 0.90 (0.57, 1.41) Fatal MI: 0.9% (15/1654) vs 1.0% (17/1650) vs 1.3% (22/1649) vs 1.0% (16/1649) RR = 0.77 (0.41, 1.45) Non-fatal MI: 2.0% (33/1654) vs 1.1% (18/1650) vs 1.0% (17/1649) vs 1.8% (29/1649) RR = 1.06 (0.55, 2.05) Other vascular events: 2.1% (35/1654) vs 1.3% (21/1650) vs 2.3% (38/1649) vs 3.3% (54/1649) RR = 0.55 (0.33, 0.94); NNT = 100 (53, 919) All ischaemic events: 16.4% (271/1654) vs 12.5% (206/1650) vs 16.1% (266/1649) vs 18.6% (307/1649) RR = 0.77 (0.65, 0.92); NNT = 27 (17, 79) Non-fatal ischaemic events: 12.8% (212/1654) vs 9.3% (153/1650) vs 12.3% (203/1649) vs 15.1% (249/1649) RR = 0.75 (0.62, 0.92); NNT = 33 (19, 108) Fatal ischaemic events: 5.7% (95/1654) vs 4.8% (80/1650) vs 5.3% (88/1649) vs 5.5% (90/1649) RR = 0.91 (0.68, 1.22) Vascular death: 7.6% (125/1654) vs 7.1% (117/1650) vs 7.2% (118/1649) vs 7.5% (124/1649) RR = 0.99 (0.77, 1.27) Vascular events: 19.6% (324/1654) vs 14.9% (246/1650) vs 19.0% (314/1649) vs 21.9% (361/1649) RR = 0.78 (0.67, 0.91); NNT = 24 (15, 64)
Juergens et al., 2004 (23), Australia (poor)	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
ESPS-2 authors, 1997(38), International, ESPS-2 (good)	Monitored; Reported spontaneously by patient	Dipyridamole vs Dipyridamole + Aspirin vs Aspirin vs Placebo GI event: 30.5% (505/1654) vs 32.8% (541/1650) vs 30.4% (502/1649) vs 28.2% (465/1649) Nausea: 14.8% (245/1654) vs 15.4% (254/1650) vs 12.4% (204/1649) vs 13.7% (226/1649) Dyspepsia: 16.6% (274/1654) vs 17.6% (290/1650) vs 17.2% (283/1649) vs 16.1% (266/1649) Vomiting: 7.2% (119/1654) vs 8.1% (133/1650) vs 5.6% (93/1649) vs 6.6% (109/1649) Gastric pain: 14.5% (240/1654) vs 16.6% (274/1650) vs 14.7% (242/1649) vs 13.3% (219/1649) Diarrhea: 15.4% (254/1654) vs 12.1% (199/1650) vs 6.6% (109/1649) vs 9.3% (154/1649) Headache: 37.2% (615/1654) vs 38.2% (630/1650) vs 33.1% (546/1649) vs 32.4% (534/1649) Bleeding any site (total): 4.7% (77/1654) vs 8.7% (144/1650) vs 8.2% (135/1649) vs 4.5% (74/1649) Dizziness: 30.1% (498/1654) vs 29.5% (486/1650) vs 29.2% (481/1649) vs 30.9% (509/1649)
Juergens et al., 2004 (23), Australia (poor)	Monitored, Reported spontaneously by patient. dx of recurrent MI-increase of >30% in the CK concentration above baseline. CK and CK-MB measurements were performed routinely on all pts the morning after the procedure and more frequently if there was a clinical suspicion of an adverse cardiac event. Occurrences of thrombotic stent occlusion (TSO), defined angiographically as total occlusion of the stented segment, were also note. Routine blood count analysis was not performed as part of the trial after hospital discharge, but when incidental blood tests were performed, results were ascertained. Pt were contacted by telephone at 2 wks and 4 wks to assess the presence of any adverse events.	Ticlopidine + Aspirin vs Clopidogrel + Aspirin Any non-cardiac event: 3.9% (6/153) vs 1.9% (3/154) Bleeding: 0.7% (1/153) vs 0.6% (1/154) Dermatological:1.3% (2/153) vs 0% (0/154) Gastrointestinal: 1.3% (2/153) vs 0.0% (0/154) Haemorrhageic complications: 0.0% (0/153) vs 0.6% (1/154) Vascular complication: 1.3% (2/153) vs 1.3% (2/154)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
ESPS-2 authors, 1997(38), International, ESPS-2 (good)		External audit was brought in --which also failed to establish guilt or innocence. A definitive decision could only be made by the Steering Committee once the compliance assays had been conducted. The initial power study for ESPS-, fixed to 80% for a risk reduction of 30% at the alpha level - 0.05, led to a total sample size of 5000 pts (1250/group) based on the best estimations availble at the time. An interm analysis was done per protocol and the estimates were changed, characterised by a lower drop out rate and a lower risk reduction (25%). Rerunning the simulation led to a new sample size of about 7000 pts (1750/group). ESPS 2 was designed to have sufficient statistical power only for the whole group and not for subgroup analysis. Data in this report is analysed for the overall tx groups, the only exception beign a few subgroups which were defined a priori as baseline risk factors for stroke and which were confirmed by the Cox's model to be independent risk variables for stroke occurrence.
Juergens et al., 2004 (23), Australia (poor)		

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period
Mehta, 2001 (8), International, PCI-CURE (good)	RCT then 2-4 week open-label following PCI and then resumed double blind treatment for a mean of 8 months	see CURE trial--symptoms indicative of ACS within the past 24 hours and no ST-segment elevation >1 mm on ECG. Other ECG evidence of new ischemia or concentrations of cardiac enzymes (including troponin) at least 2x the upper limit of normal was required. Of note, initially patients above the age of 60 with no new ECG changes but with objective evidence of ischemia were included in the trial. However, after a review of the overall event rates among the first 3000 pts, the steering committee recommended that all pts have either ECG changes or a cardiac enzyme rise at entry.	clopidogrel 300mg x 1 loading dose and then 75mg daily + ASA 75mg-325mg daily vs. matching placebo + ASA 75mg-325mg daily x 3-12 months (mean of 8 months)	None
Piamsomboon et al., 2001 (22), Bangkok, Thailand (poor)	RCT,one-center	June 1999-December 2000-symptomatic coronary artery disease or documented myocardial ischemia by treadmill exercise test or myocardial perfusion scan and coronary angiographic evidence of ≥ 70 % stenosis in diameter. Pts underwent coronary stenting	Clopidogrel 300mg loading dose 4 hrs prior to procedure, followed by 75mg once daily x 4 wks + ASA 300mg twice a day x 4 wks vs. ticlopidine 250 mg twice a day starting 2 d prior to stent and continued x 4 wks + ASA 300mg twice a day x 4 wks. At 4 wks follow-up, ASA was decreased to 300mg once daily if there was no contraindication.	None

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(6) Allowed other medications/ interventions	(7) Method of Outcome Assessment and Timing of Assessment
Mehta, 2001 (8), International, PCI-CURE (good)	glycoprotein 2b/3a during PCI . (About 25% of pts in each group received open-label thienopyridines before PCI and more than 80% received them afterwards for a median of 30 days.	MI defined as the presence of at least 2 of the 3 following: ischaemic symptoms; cardiac enzyme concentration at least 3X ULN if within 48 h of PCI, and 2X ULN therafter; or new ECG changes compatible with MI. Urgent target-vessel revascularization within 30 d of PCI was defined as a second PCI or any coronary artery bypass graft procedure done on a non-elective basis in the target vessel because of recurrent myocardial ischaemia. Death, MI, refractory ischaemia, and major and life-threatening bleeding were adjudicated by a committee blinded to treatment. Mean follow-up = 8 mos post-PCI. Follow-up assessments will occur at baseline, hospital discharge, and at 1 month and 3 mos (with additional f/u visits at 6, 9, and 12 mos for pts randomized early in the study per CURE Study Investigators (see Eur Heart J 2000; 21: 2033-2041) Of note, (information provided in the rationale, design and baseline characteristic article for CURE trial (Eur Heart J 2000; 21: 2033-2041), and independent Data and Safety Monitoring Board (DSMB) monitored the progress of all aspects of the study. For efficacy, the co-primary outcomes will b
Piamsomboon et al., 2001 (22), Bangkok, Thailand (poor)	100 U/kg bolus dose of heparin was given initially, a repeated dose was given as needed to keep the activated clotting time ≥ 250 seconds.	An on-line quantitative angiographic analysis system was used to analyze the coronary artery pre and post-procedure. Follow-up with referring physician at 4 weeks after procedure for clinical assessment and completed blood count.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized
Mehta, 2001 (8), International, PCI-CURE (good)	PCI population: Mean age 61.6 ± 11.2 in the clopidogrel group and 61.4 ± 10.9 in the placebo group. 30% in both groups were women; 70% males. Ethnicity not reported	19% were diabetics; 26% vs. 27.3% in the placebo and clopidogrel groups respectively had a previous MI; 13.8% in the placebo and 13.4% in the clopidogrel group had a previous PCI. 13% and 12% in the placebo and clopidogrel group had a previous CABG, respectively; ~30 were smokers in both groups	Number screened not reported /(12562 pts were randomized into CURE) 2658 pts of the CURE population underwent PCI and were eligible/2658 were enrolled/randomized-N/A
Piamsomboon et al., 2001 (22), Bangkok, Thailand (poor)	60 ± 9 years ; 84% male and 16% female in ticlopidine + ASA group; 61 ± 10 years; 73% male and 27% female in clopidogrel + ASA group. Ethnicity not reported	Ticlopidine + ASA group: 29% (n=9) acute MI, 32% (n= 10) unstable angina, 48% (n= 15) HTN; 39% (12) hypercholesterolemia, 45% (n=14) smoking; 29% DM (n=9), 19% (n=6) previous MI, 6% (n= 2) previous revascularization. Clopidogrel + ASA group: 30% (n=11) acute MI, 27% (n= 10) unstable angina, 38% (n= 14) HTN; 27% (10) hypercholesterolemia, 27% (n=10) smoking; 38 % (n=14) DM, 14% (n= 5) previous MI,11% (n= 4) previous revascularization	Number screened not reported/ number eligible not reported/ 68 enrolled/ 68 randomized

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(11) Number withdrawn/ lost to fu/analyzed	(12a) Results
Mehta, 2001 (8), International, PCI-CURE (good)	0 drop-outs/0 lost to f/u/analyzed	**Clopidogrel vs Placebo** *Outcomes at 30 days* CV death, myocardial infarction, urgent revascularisation: 4.5% (59/1313) vs 6.4% (86/1345) RR = 0.70 (0.50, 0.97); NNT = 53 (28, 560) CV death, MI: 2.9% (38/1313) vs 4.4% (59/1345) RR = 0.66 (0.44, 0.99); NNT = 67 (34, 1405) CV death: 1.1% (14/1313) vs 1.0% (13/1345) RR = 1.10 (0.52, 2.35) MI: 2.1%(28/1313) vs 3.8% (51/1345) RR = 0.56 (0.35, 0.89); NNT = 60 (34, 268) Q-wave MI: 0.8% (11/1313) vs 2.4% (32/1345) RR = 0.35 (0.18, 0.70); NNT = 65 (40, 170) Urgent revascularisation: 1.9% (25/1313) vs 2.8% (38/1345) RR = 0.67 (0.41, 1.11)
Piamsomboon et al., 2001 (22), Bangkok, Thailand (poor)	0 withdrawn or lost to f/u	**Ticlopidine + Aspirin vs Clopidogrel + Aspirin** *Outcomes at a 1 month* Major cardiovascular event: 0% (0/31) vs 0% (0/37) RR = NC Death: 6.5% (2/31) vs 0% (0/37) RR = NC *Outcomes at 6 months* Major cardiovascular events: 3.6% (1/31) vs 2.7% (1/37) RR = 1.19 (0.08, 18.31) Recurrent angina pectoris: 3.6% (1/31) vs 16.5% (5/37) RR = 0.24 (0.03, 1.94) In-stent restenosis: 3.6% (1/31) vs 13.3% (4/37) RR = 0.30 (0.04, 2.53)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Mehta, 2001 (8), International, PCI-CURE (good)	*Outcomes at 12 months* CV death, MI, urgent revascularisation: 6.0% (79/1313) vs 8.0% (108/1345) RR = 0.75 (0.56, 1.00) CV death, MI: 18.3% (240/1313) vs 21.7% (292/1345) RR = 0.83 (0.70, 0.99); NNT = 29 (15, 254) CV death: 2.4% (32/1313) vs 2.3% (31/1345) RR = 1.07 (0.65, 1.75) MI: 4.5% (59/1313) vs 6.4% (85/1345) RR = 0.71 (0.51, 0.99); NNT = 55 (28, 912) Q-wave MI:1.5% (20/1313) vs 3.5% (47/1345) RR = 0.43 (0.26, 0.73); NNT = 51 (32, 127) Any revascularisation: 14.2% (186/1313) vs 17.1% (230/1345) RR = 0.82 (0.68, 1.00)
Piamsomboon et al., 2001 (22), Bangkok, Thailand (poor)	

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Mehta, 2001 (8), International, PCI-CURE (good)	Monitored- Major bleeding was defined as bleeding that was significantly disabling, intraocular, or requiring at least 2 units of blood. Major bleeding was subclassified as life threatening if it was fatal, if it led to a decrease in hemoglobin concentration of 50 g/L, if it caused significant hpotension requiring IV inotropes or surgical intervention, if it resulted in symptomatic intracranial hemorrhage, or if it necessitated transfusion of 4 or more units of blood. Monitor bleeding was defined as other bleeding that led to interruption of study medication. Major and life-threatening bleeding (as well as death, Mi, refractory ischemia) were adjudicated by a committee that were blinded to treatment.	Clopidogrel vs Placebo Major bleeding: 2.7% (36/1313) vs 2.5% (33/1345) Life-threatening bleeding: 1.2% (16/1313) vs 1.3% (18/1345) Non-life-threatening bleeding: 1.5% (20/1313) vs 1.1% (15/1345) Minor bleeding: 3.5% (46/1313) vs 2.1% (28/1345) Blood transfusions of 2 or more units: 2.1% (28/1313) vs 2.0% (27/1345)
Piamsomboon et al., 2001 (22), Bangkok, Thailand (poor)	Monitored- Patients were instructed to attend f/u with their referring MD at 4 weeks after the procedure for clinical assessment and complete blood count. Clinical assessment was done ever 8 weeks. Acute stent thrombosis-thrombotic stent closure within 24 hours after the stent implantation. Subacute stent thrombosis was defined as thrombotic stent closure more than 24 hours after the stent imlantation. Major CV events were defined as CV death, stroke, acute nonfatal MI and unstable angina. Acute MI was diagnosed when there were two of the following: characteristic ischemic pain for ≥ 20 minutes, elevation of C, CK-MB more than twice the upper limit, and new electrocardiographic change. Mj bleeding was defined as bleeding which required blood transfusion. Restenosis was defined as a diameter stenosis more than 50%	Ticlopidine + Aspirin vs Clopidogrel + Aspirin At 1 month follow-up Major bleeding: 3.2% (1/31) vs 5.4% (2/37) Minor bleeding: 0.0% (0/31) vs 5.4% (2/37) Rash: 3.2% (1/31) vs 0% (0/37)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Mehta, 2001 (8), International, PCI-CURE (good)		334/1313 took open-label thienopyridine before PCI and 969/1313 received study drug up to PCI per protocol analysis in the clopidogrel group. 329/1345 took open-label thienopyridine before PCI (mean of 10 days) while 1016/1345 received study drug up to PCI per protocol analysis in the placebo group. Benefit seen at 30 days after PCI may be an underestimate of the true treatment effect, since ~25% of pts in boths groups also received open-label thienopyridine befor ethe procedure.--although analysis was also done excluding those pts that had open-label thienopyridine--42% reduction in the primary otucome was seen. Investigators did not routinely screen for symptomless increases in periprocedural cardiac enzme concentrations, and so some smaller, non-Q wave Mi might not have been documented. However, the study was randomized and DB so authors stated that this approach should still lead to an unbiased estiamte of the effect of clopidogrel. There was a reduction in the use of IV glycoprotein 2b/3a antagonist during PCI in the clopidogrel group. Baseline characteristics of the study population are consistent with at least a moderate risk group of patients with ACS per authors.
Piamsomboon et al., 2001 (22), Bangkok, Thailand (poor)		

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period
Cure Trial Investigators, 2001 (6), International, CURE (good)	RCT, DB, PC between Dec. 1998 and Sept. 2000, multicenter, international. See #117 for rationale, design and baseline characteristics	hospitalized within 24 hours after onset of symptoms and did not have ST-segment elevation. Initially pts >60 yrs with no new ECG changes but with a history of CAD were included But after a review of the overall rates of events among the first 3000 patients, it was recommended that only pts who had either ECG changes or an elevation in the serum level of cardiac enzymes or markers at entry would be included.	clopidogrel 300mg loading dose followed by 75 mg/day plus ASA 75 to 325 mg daily) or matching placebo plus ASA, 75 to 325mg daily x 3-12 months (mean duration of treatment, 9 months.	None
Steinhuble et al., 2002 (9) North America, CREDO (good)	RCT, DB, PC between June 1999 through April 2001	symptomatic coronary artery disease with objective evidence of ischemia (i.e. symptoms of angina pectoris, positive stress test results, or dynamic electrocardiographic [ECG changes); were referred for PCI or thought to be at high likelihood for requiring PCI with either stent placement with or without conventional balloon angioplasty or another revascularization device; at least 21 years old; provided informed consent before randomization; and agreed to comply with all protocol-specified procedures	3-24 hrs before PCI: 300mg loading dose of clopidogrel + ASA 325mg (pretreatment group) or matching placebo + ASA 325mg. After PCI: both groups received 75mg/day of clopidogrel and 325mg/day of ASA through day 28. After 28 days: (pretreatment group) 75mg daily of clopidogrel + ASA 81-325mg/day (at discretion of the investigator) vs. matching placebo + ASA 81 -325mg/day (at discretion of the invest.) x 12 mos	None

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(6) Allowed other medications/ interventions	(7) Method of Outcome Assessment and Timing of Assessment
Cure Trial Investigators, 2001 (6), International, CURE (good)	Medications at time of randomization: 66% on ASA, 37% ACE inhibitor, 58.6% BB, 28.3% calcium-channel blockers, 25.4% lipid-lowering agents	Follow-up assessments occurred at discharge, at one or three months, and then every 3 months until the end of the study.
Steinhuble et al., 2002 (9) North America, CREDO (good)	20% of all pts could be prespecified at the time of randomization to receive a Gp2b/3a receptor antagonist (primarily abciximab) at the time of PCI. Bail-out GP 2b/3a inhibitor use was allowed for all pts at the discretion of the MD performing Pick	Follow-up assessment was performed on days 2, 28, 60, 180, 270 and 365 following randomization

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized
Cure Trial Investigators, 2001 (6), International, CURE (good)	Clopidogrel group: 64.2± 11.3 years; 38.7% female, 61.3% males. Placebo group: 64.2 ± 11.3 years; 38.3% females, 61.7% females. Ethnicity not reported	32.4% MI, 17.7% CABG or PTCA, 4% stroke, 7.6% heart failure, 59.9% HTN; 22.4% DM; 60.6% current or former smoker in Clopidogrel group In Placebo: 32% MI, 18.1% CABG or PTCA, 3.7% stroke, 7.8% heart failure, 57.8% HTN; 22.8% DM; 60.9% current or former smoker	Number screened not reported/number eligible not reported/number enrolled not reported/12,562 randomized
Steinhuble et al., 2002 (9) North America, CREDO (good)	Clopidogrel Group: 61.5± 11.2, 29.3% female; 70.7% male, 88.2% white; Placebo Group: 61.8± 11.0, 27.9% female, 72.1% male, 89.5% white	34% previous MI,6.7 % previous stroke, 26.45% DM, 10% PVD, 68.5% HTN, 30.8% smoking (within past year); 74.7% hyperlipidemia	17898 screened/2116 eligible/2116 enrolled/2116 randomized

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(11) Number withdrawn/ lost to fu/analyzed	(12a) Results
Cure Trial Investigators, 2001 (6), International, CURE (good)	6 pts in the clopidogrel and 7 pts in the placebo lost to follow-up	**Clopidogrel vs Placebo** *Outcomes at a 12 months* Nonfatal MI, stroke, or death from cardiovascular cause: 9.3% (582/6259) vs 11.4% (719/6303) RR = 0.82 (0.73, 0.90); NNT = 47 (32, 96) Nonfatal MI, stroke, death from cardiovascular causes, or refractory ischemia: 16.5% (1035/6259) vs 18.8% (1187/6303) RR = 0.88 (0.81, 0.95); NNT = 40 (28, 104) Death from cardiovascular causes: 5.1% (318/6259) vs 5.5% (345/6303) RR = 0.93 (0.80, 1.10) MI: 5.2% (324/6259) vs 6.7% (419/6303) RR = 0.78 (0.68, 0.90); NNT = 68 (44, 155) Q-wave MI: 1.9% (116/6259) vs 3.1% (193/6303) RR = 0.61 (0.48, 0.76); NNT = 83 (57, 150) MI non-q-wave: 3.5% (216/6259) vs 3.8% (242/6303) RR = 0.90 (0.75, 1.08)
Steinhuble et al., 2002 (9) North America, CREDO (good)	clopidogrel group: 50 discontinued study drug prior to day 28; 411 permanently discontinued study drug, 38 no f/u at 1 y(28 withdrew consent, 8 lost-to f/u, 2 other). Placebo group: 44 discontinued study drug prior to day 28; 420 permanently discontinued study drug, 48 no f/u at 1 y (31 withdrew consent, 15 lost-to f/u, 2 other)	**Clopidogrel vs Placebo** *Outcomes at a 12 months* Death, MI, stroke: 8.5% (89/1053) vs 11.5% (122/1063) RR = 0.73 (0.57, 0.95); NNT = 33 (18, 210) Death, MI: 8.0% (84/1053) vs 10.4% (111/1063) RR = 0.76 (0.58, 1.00)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Cure Trial Investigators, 2001 (6), International, CURE (good)	Stroke: 1.2% (75/6259) vs 1.4% (87/6303) RR = 0.87 (0.64, 1.18) Refractory ischemia: 8.7% (544/6259) vs 9.3% (587/6303) RR = 0.93 (0.83, 1.04) Refractory ischemia during initial hospitalization: 1.4% (85/6259) vs 2.0% (126/6303) RR = 0.68 (0.52, 0.89); NNT = 156 (92, 521) Refractory ischemia after discharge: 7.6% (459/6259) vs 7.6% (461/6303) RR = 1.00 (0.89, 1.14) Death from noncardiovascular causes: 0.7% (41/6259) vs 0.7% (45/6303) RR = 0.92 (0.60, 1.40)
Steinhuble et al., 2002 (9) North America, CREDO (good)	Death: 1.7% (18/1053) vs 2.3% (24/1063) RR = 0.76 (0.41, 1.39) MI: 6.6% (70/1053) vs 8.5% (90/1063) RR = 0.79 (0.58, 1.06) Stroke: 0.9% (9/1053) vs 1.1% (12/1063) RR = 0.76 (0.32, 1.79) Revascularization any tvr: 13.2% (139/1053) vs 13.5% (144/1063) RR = 0.97 (0.78, 1.21) Revascularization urgent tvr: 2.0% (21/1053) vs 2.2% (23/1063) RR = 0.92 (0.51, 1.66) Any revascularization: 21.4% (225/1053) vs 21.0% (223/1063) RR = 1.01 (0.86, 1.20)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Cure Trial Investigators, 2001 (6), International, CURE (good)	Monitored-Data were periodically reviewed by an independent data and safety monitoring board. All primary outcomes and life-threatening and mj bleeding complications were adjudicated	Clopidogrel vs Placebo Major bleeding: 3.7% (232/6259) vs 2.7% (170/6303) Life-threatening bleeding: 2.2% (135/6259) vs 1.8% (112/6303) Transfusion of 2 or more units of blood: 2.8% (177/6259) vs 2.2% (137/6303) Early major bleeding: 2.0% (125/6259) vs 1.5% (95/6303) Late major bleeding: 1.7% (106/6259) vs 1.1% (69/6303) Major bleeding after CABG: 1.3% (81/6259) vs 1.1% (69/6303) Minor bleeding: 5.1% (322/6259) vs 2.4% (153/6303) Vascular complication: 1.3% (2/154) vs 1.3% (2/153) Thrombocytopenia: 0.4% (26/6259) vs 0.4% (28/6303) Neutropenia: 0.1% (8/6259) vs 0.1% (5/6303)
Steinhuble et al., 2002 (9) North America, CREDO (good)	Monitored: All potential events were identified by site investigators or through screening of protocol-specified ECGs and laboratory test, blinded to treatment assignments. An independent clinical events committee, also blinded to treatment assignment, adjudicated all outcome events, and all analyses were based on the committee's classification of the end points.	Clopidogrel vs Placebo Major bleeding: 8.8% (93/1053) vs 6.7% (71/1063) Non-procedural major bleeding: 1.2% (13/1053) vs 0.8% (8/1063) Procedural major bleeding: 7.7% (81/1053) vs 5.9% (63/1063) Major bleeding from CABG: 6.0% (63/1053) vs 5.2% (55/1063) Major bleeding from non-CABG: 1.7% (18/1053) vs 0.8% (8/1063) Minor bleeding: 5.3% (56/1053) vs 5.6% (59/1063) Non-procedural minor bleeding:0.7% (7/1053) nvs 0.8%(8/1063) Procedural minor bleeding:4.7% (50/1053) vs 4.9% (52/1063) Minor bleeding from CABG: 2.3% (24/1053) vs 2.8% (30/1063) Minor bleeding from non-CABG: 2.5% (26/1053) vs 2.1% (22/1063)

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Cure Trial Investigators, 2001 (6), International, CURE (good)		
Steinhuble et al., 2002 (9) North America, CREDO (good)		

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(2) Study Design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/ Washout Period
Hass et al., 1989 (12), North America, TASS (good)	RCT, MC	3 months before entry into the study they had ad 1 or more of the following: TIA lasting less than 24 hours and followed by completely recovery); amaurosis fugax; reversible ischemic neurologic deficit; or minor stroke between 2/82-5/86.	Ticlopidine 250mg twice a day or ASA 1300mg daily x2-6 years	None
Rupprecht et al., 1998 (31), Germany (poor)	R, single center	Successful implantation of a single Palmaz-Schatz stent if they were at low risk for subacute stent thrombosis. This included a vessel diameter of the stented segment of ≥ 3.0 mm, absence of thrombus formation before and after stent placement, a TIMI grade 3 blood flow, absence of a residual dissection, and absence of a residual lesion >20% within or adjacent to the stent	pretreated with 100mg aspirin/day for at least 1 wk before randomization; then randomized to either: Group A: ASA 300 mg/day plus ticlopidine 2 X 250mg/day; Group B: ticlopidine 2 x 250 mg/day; Group C: aspirin 300 mg/day x 4 wks. After initial 4 wk treatment period, ASA 100mg/day was continued	None

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(6) Allowed other medications/ interventions	(7) Method of Outcome Assessment and Timing of Assessment
Hass et al., 1989 (12), North America, TASS (good)	Not reported	Follow-up one month after randomization and then at 4 month intervals throughout the trial. Patients were questioned about new symptoms, new medical problems, ADR, compliance. Blodd and urine samples were obtained. During the first three months, CBC were done every 2 weeks
Rupprecht et al., 1998 (31), Germany (poor)	All received heparin 10 000 IU during PCI procedure and then continued x 24 hours to maintain a aPTT of 60 to 90 seconds. All patients were pretreated with 100mg ASA per day for at least 1 week before randomization.	Laboratory studies immediately after randomization, on day 7 and on day 14 of treatment. Platelet aggregatation, platelet cont and platelet activation (evaluated by flow cytometry measurement) were done as well as fibrinogen binding.

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized
Hass et al., 1989 (12), North America, TASS (good)	Ticlopidine group: mean age 62.7 ± 9.4; male%/female% 64/36, 80% white. In aspirin group: mean age 63.2± 9.3; male% female% 65/35, 81% white.	T vs. ASA group: 41% vs. 42% smokers; 18% stable angina in both groups; 1% unstable angina in both groups; 16% and 17% MI, 19% and 20% DM, 14% and 15% PVD. 40 and 41% hypercholesterolemia	8814 screened/3069 eligible/3069 enrolled/3069 randomized
Rupprecht et al., 1998 (31), Germany (poor)	Age Group A: 59 ±8; 76% male, 24% female, Ethnicity, not reported. Group B: 59±10; 70% male, 30% female, Ethnicity not reported. Group C: 59±9; 75% male, 25% female, Ethnitiicy not reported.	Group A: 19% diabetes; 48% hypercholesterolemia, 33% smoker, 19% previos MI, 19% orevious PTCA, 10% unstable angina, 38% unstable angina. Group B: 20% diabetes, 40% HTN, 45% hypercholesterolemia,40% smoker, 25% previous MI, 15% previous PTCA, 5% previous CABG, 45% unstable angia. Group C:15% diabetes, 45% hypertension, 40% hypercholesterolemia, 35% smoking, 20% previous MI, 15% previous PTCA, 10% previous CABG	unknown/unknown/unknown/61

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(11) Number withdrawn/ lost to fu/analyzed	(12a) Results
Hass et al., 1989 (12), North America, TASS (good)	46 (3%) ticlopidine group and 38 (2%) ASA group lost to follow-up. 51.6% patients in the ticlopidine and 47% in the ASA groups prematurely terminated study medication primarily AE (20.9% T group and 14.5% ASA group (p<0.05) and noncompliance 13.6 vs. 13.3	**Ticlopidine vs Aspirin** *Outcomes at 60 months* Death from all causes or nonfatal stroke: 20.0% (306/1529) vs 22.7% (349/1540) RR = 0.88 (0.77, 1.01) Nonfatal stroke: 10.2% (156/1529) vs 12.3% (189/1540) RR = 0.83 (0.68, 1.02) Fatal stroke: 1.0% (16/1529) vs 1.5% (23/1540) RR = 0.70 (0.37, 1.32) Death from other causes: 8.8% (134/1529) vs 8.9% (137/1540) RR = 0.99 (0.78, 1.24) Fatal or nonfatal stroke: 11.2% (172/1529) vs 13.8% (212/1540) RR = 0.84 (0.69, 1.01); NNT = 40 (21, 561)
Rupprecht et al., 1998 (31), Germany (poor)	unknown	**No outcome data reported.**

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(12b) Results - continued
Hass et al., 1989 (12), North America, TASS (good)	Death from all causes: 11.4% (175/1529) vs 12.7% (196/1540) RR = 0.90 (0.74, 1.08) Cerebrovascular: 1.4% (22/1529) vs 1.8% (28/1540) RR = 0.79 (0.45, 1.38) Cardiovascular: 5.8% (89/1529) vs 5.1% (78/1540) RR = 1.15 (0.86, 1.54) Acute myocardial infarction: 1.4% (21/1529) vs 0.9% (14/1540) RR = 1.51 (0.77, 2.96) Sudden death: 2.9% (44/1529) vs 2.7% (41/1540) RR = 1.08 (0.71, 1.64) Other cardiovascular: 1.6% (24/1529) vs 1.5% (23/1540) RR = 1.05 (0.60, 1.85)
Rupprecht et al., 1998 (31), Germany (poor)	**No outcome data reported.**

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(13) Method of adverse effects assessment?	(14) Adverse Effects Reported
Hass et al., 1989 (12), North America, TASS (good)	Not reported	Ticlopidine vs Aspirin Diarrhea: 20.4% (310/1518) vs 9.8% (150/1527) Dyspepsia: 12.6% (191/1518) vs 13.8% (210/1527) Nausea: 11.1% (169/1518) vs 10.2% (156/1527) Gastrointestinal pain: 7.2% (110/1518) vs 10.0% (153/1527) Gastritis: 0.9% (13/1518) vs 1.7% (26/1527) Gastrointestinal hemorrhage: 0.5% (7/1518) vs 1.4% (21/1527) Peptic ulcer: 0.8% (12/1518) vs 2.9% (45/1527) Rash: 11.9% (180/1518) vs 5.2% (80/1527) Urticaria: 2.0% (30/1518) vs 0.3% (5/1527) All hemorrhagic: 9.0% (137/1518) vs 10.0% (152/1527) Severe neutropenia: 0.9% (13/1518) vs 0.0% (0/1527)
Rupprecht et al., 1998 (31), Germany (poor)	Monitored	one major bleeding event with a drop in Hgb concentration by 4mg/dL at groin puncture site of one patient in group C

MI=Myocardial Infarction

Evidence Table A1. Randomized Controlled Trials

(1) Author Year Country Trial Name (Quality Score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Hass et al., 1989 (12), North America, TASS (good)		
Rupprecht et al., 1998 (31), Germany (poor)		

MI=Myocardial Infarction

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Mueller C. et al., 2003 (27), Germany and Switzerland	Yes-pre-specified randomization sequence	Yes	Yes	Yes- "consecutive pts with successful stent implantation" were randomized
Atmaca et al., 2002 (25), Ankara, Turkey	Yes, closed envelope system without patient stratification	Yes-closed envelope system without patient stratification	C Group had higher frequency lesion in the RCA p= <0.02, and T Group had a higher ejection fraction <0.04	Yes-undergoing elective single vessel PTCA. Inclusion criteria pts with Canadian Cardiac Society Class-II stable angina pectoris and de novo lesions in large native coronary arteries.
Taniuchi et al., 2001 (30), USA	Method not reported other than it stated it used a randomized protocol	Method not reported	yes except the C group had more thrombus on angiography than the T group p= 0.009	Yes-successful implantation (<20% residual stenosis, with TIMI2 or TIMI 3 flow) of an FDA-approved stent in a native coronary artery or in a CABG)
Mueller C. et al., 2000 (26), Germany	No-unblinded	Yes-prespecified randomization sequence	Yes	Yes-successful implantation (<50% residual stenosis without acute complications in the catheter lab resulting in death or emergency CABG)

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Leon et al., 1998 (32), USA	Yes-used a prespecified randomization sequence to one of the 3 antithrombotic-drug regimens, according to clinical site and history of DM	Yes	Yes	Yes
Bertrand et al., 2000 (29), Europe CLASSICS	Yes	Yes	Yes	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Hall et al., 1996 (28), Milan, Italy and Tokyo, Japan	Yes-using a standard list of random numbers	Method not reported-did not indicate whether the standard list of random numbers were unreadable till allocation	No, incidence of total occlusions at baseline angiography was higher in the ASA group (15%) than in the T-ASA group 8%, p<.05. A higher percentage of pts had previous CABG or DM in T+ASA group (11%, 16% respectively) compared with ASA only group (3%, 6%) p= .02 and .01	Yes
Diener et al., 2004 (11), 28 countries including multiple ones in Europe, USA, Spain	Yes	Yes-centrally with an interactive voice-response system (by phone) and was based on a computer-generated list of treatment numbers.	Yes	Yes-

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Gorelick et al., 2003 (41), 62 academic and community hospitals in USA	Yes -1:1 and the sequence was stratified by site to balance the treatment groups. Local study site personnel called a automated telephone registration system to register a study participant	Yes	yes	yes
CAPRIE Steering Committee, 1996 (13), International	Yes	Yes	Yes	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Diener et al., 1996 (10), multicenter-59 sites in 13 countries between 2/89 and 3/95	Yes	Yes	Yes	Yes
ESPS-2 Authors, 1997 (38), multicenter-59 sites in 13 countries	Yes-randomized to tx groups according to a minimization technique which took into account the initial diagnosis	Yes-randomization was performed by a central computer, accessible to the centers day and night, and requiring the entry by the trialist of inclusion and exclusion criteria before allocating a randomization number to the pt.	Yes	Yes
Juergens C et al., 2004 (23), single center, Australia	Yes-sealed envelope system	No-sealed envelope	Yes	Yes
Mehta et al., 2001 (8), International, (PCI-CURE)(good)	Yes	Yes	Yes-although of note, before PCI, fewer pts on clopidogrel than on placebo had MI or refractory ischemia, p=0.008.	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Piamsomboon et al., 2001 (22), Bangkok, Thailand, single center (poor)	No-?unblinded,	Not reported	Mean lumen diameter in the ticlopidine groups was smaller than the clopidogrel group 2.75 ± 0.33 vs. 3.00 ±0.52, p= 0.01)	Yes
Cure Investigators et al., 2001 (6), International	Yes	Yes	Yes	Yes
Fiotti et al., 2003 (46), Italy, single-centered (fair-poor)	No-method not reported	No-sealed envelope	No	Yes
Steinhuble et al., 2002 (9), North America, CREDO (good)	Yes	Yes	less use of statins and calcium channel blockers in the clopidogrel arm 53.5 vs. 57.3, p=.08; 25.5 vs. 29.4, p=.05 respectively	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Hass et al., 1989 (12), North America, TASS (good)	randomized by a private independent, nonprofit organization--randomization within each center was stratified on the basis of 3 factors: history of ischemic CV disease, occurrence of a moderate or major stroke >3 months before entry, and the pt's sex.	Not reported	Yes	Yes
Juergens C et al., 2004 (23), Australia (poor)	Yes-sealed envelope system	No	Yes	Yes-not in detail (successful stent deployed)
Rupprecht et al., 1998 (31), Germany (poor)	Not reported	Not reported	Yes	Yes

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**
Mueller C. et al., 2003 (27), Germany and Switzerland	Yes-treatment was not blinded, but all end points were adjudicated by a clinical events committee whose members were unaware of the pts' treatment assignments.	No	No	Yes/Not applicable/Not reported/Not reported
Atmaca et al., 2002 (25), Ankara, Turkey	Yes-but methods not described	Yes	Yes	yes/not applicable/Yes/not reported
Taniuchi et al., 2001 (30), USA	?No	No	No	Yes-1367 screened/1016 randomized; the primary end point, failure to complete 2 weeks of concurrent therapy with ASA was reached in 3.64% (19 pts) in the T group and in 1.62% (8 pts) in C group (p=0.043).
Mueller C. et al., 2000 (26), Germany	Yes-endpoints were adjudicated by a clinical-events committee whose members were unaware of the pts tx assignments	No	Not reported	Yes/Not applicable/Not reported/No

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**
Leon et al., 1998 (32), USA	Yes-treatment was not blinded, but all end points were adjudicated by a clinical events committee whose members were unaware of the pts' treatment assignments.	No	No	Not reported/Not applicable. Not reported. Not reported
Bertrand et al., 2000 (29), Europe CLASSICS	Yes	yes	Yes	Yes/ (1 withdrew consent before taking his first study med--not included in data) Not applicable/Not reported/Not reported

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**
Hall et al., 1996 (28), Milan, Italy and Tokyo, Japan	Not reported	No	No	Yes/Yes/No/No=
Diener et al., 2004 (11), 28 countries including multiple ones in Europe, USA, Spain	Yes	Yes	Yes	Yes/Yes/Yes/No

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**
Gorelick et al., 2003 (41), 62 academic and community hospitals in USA	yes-except of 1 statistician who developed the randomization algorithm	yes-	yes	Yes/Yes/No/Not reported-
CAPRIE Steering Committee, 1996 (13), International	Yes	Yes	Yes	Yes/Yes/Yes/No

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**
Diener et al., 1996 (10), multicenter-59 sites in 13 countries between 2/89 and 3/95	Yes	Yes	Yes	Yes/Yes/yes/No
ESPS-2 Authors, 1997 (38), multicenter-59 sites in 13 countries	Yes	Yes	Yes	Yes/Yes/Yes/No
Juergens C et al., 2004 (23), single center, Australia	No	No	No	yes/Not reported/Not reported/No
Mehta et al., 2001 (8), International, (PCI-CURE)(good)	344/1313 PC pts in the clopidogrel group and 329/1345 PCI patients in the placebo group took open label thienopyridine before PCI. Following PCI, open label continued for 2-4 weeks and then the double-blind therapy was resumed.	yes, except during the open-label time after the PCI procedure	Yes	Yes/No/No/No

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**
Piamsomboon et al., 2001 (22), Bangkok, Thailand, single center (poor)	Not reported	Not reported	Not reported	Not reported/No/Not reported/Not reported
Cure Investigators et al., 2001 (6), International	Yes-although ?success of blinding	Yes	Yes	Yes/not applicable/Yes/unsure--reasons for withdrawal not reported
Fiotti et al., 2003 (46), Italy, single-centered (fair-poor)	No	No	No	Yes/not applicable/not reported/not reported
Steinhuble et al., 2002 (9), North America, CREDO (good)	Yes	yes	Yes	Yes/Not applicable/Yes/Yes

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**
Hass et al., 1989 (12), North America, TASS (good)	Yes	Yes	Yes	Yes/NA/Yes/Yes
Juergens C et al., 2004 (23), Australia (poor)	N0	No	No	yes/not applicable/yes/unsure
Rupprecht et al., 1998 (31), Germany (poor)	No	No	No	Not reported/Not applicable/Not reported/Not reported

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**	**(11) Post-randomization exclusions?**	**(12) Quality Rating**
Mueller C. et al., 2003 (27), Germany and Switzerland	No-	Yes	Unable to determine	fair/poor-not blinded
Atmaca et al., 2002 (25), Ankara, Turkey	No	No	see #3 answer-BL characteristics were shown after 10 patients were excluded	fair
Taniuchi et al., 2001 (30), USA	No-	Yes	Cardiac death occurred more frequently in the T group (1.53% vs. 0.61%) resulting in a higher overall rate of major adverse cardiac events (4.60% vs. 3.85%) at 30 day but neither differences reached SS.	fair
Mueller C. et al., 2000 (26), Germany	No	Yes	No	fair-unblinded and not powered to show SS difference in cardiac events

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**	**(11) Post-randomization exclusions?**	**(12) Quality Rating**
Leon et al., 1998 (32), USA	No	Yes	Yes-3 components were primarily responsible for the differences seen in the incidence of primary event: revascularization of the target lesion (p=0.002), angiographically evident thrombosis (p=0.004), and recurrent MI (p=0.01), there was also significant difference in the incidence of revascularization of the target lesion and angiographically evident thrombosis between the group assigned to ASA and T and either the group assigned to ASA only or the group assigned to ASA and W.	fair
Bertrand et al., 2000 (29), Europe CLASSICS	No	Yes	yes-except for the one that withdrew consent	Good

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**	**(11) Post-randomization exclusions?**	**(12) Quality Rating**
Hall et al., 1996 (28), Milan, Italy and Tokyo, Japan	No	yes	No	Poor
Diener et al., 2004 (11), 28 countries including multiple ones in Europe, USA, Spain	No	Yes	No	Good

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**	**(11) Post-randomization exclusions?**	**(12) Quality Rating**
Gorelick et al., 2003 (41), 62 academic and community hospitals in USA	yes--15.2% in the Ticlopidine group and 13.3% ASA group lost to f/u or voluntary withdrawal	Yes	No	Good
CAPRIE Steering Committee, 1996 (13), International	No	yes	No	Good

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**	**(11) Post-randomization exclusions?**	**(12) Quality Rating**
Diener et al., 1996 (10), multicenter-59 sites in 13 countries between 2/89 and 3/95	No	Yes	unsure	Good
ESPS-2 Authors, 1997 (38), multicenter-59 sites in 13 countries	Yes-see comments	Yes	Unsure	fair/good
Juergens C et al., 2004 (23), single center, Australia	No	yes	Unable to determine-- drug discontinuation occurred more often in the Ticlopidine group--including the composite of drug discontinuation, hemorrhage and vascular complications	poor-not randomized, open-labeled, single centered, ? Allocation method, use of GP 2B/3An varied not only the agents but the frequency. LD of clopidogrel was 150mg instead of 300mg
Mehta et al., 2001 (8), International, (PCI-CURE)(good)	No	Yes	No	Good

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**	**(11) Post-randomization exclusions?**	**(12) Quality Rating**
Piamsomboon et al., 2001 (22), Bangkok, Thailand, single center (poor)	No	Yes	No	Poor
Cure Investigators et al., 2001 (6), International	No	Yes	No	Good
Fiotti et al., 2003 (46), Italy, single-centered (fair-poor)	No	No	No	fair-poor--not randomized, open-labeled, single centered,
Steinhuble et al., 2002 (9), North America, CREDO (good)	No	Yes	No	Good

Evidence Table A2. Quality Assessment for Controlled Trials

	Internal Validity			
Author, Year Country	**(9) Loss to follow-up: differential/high?**	**(10) Intention-to-treat (ITT) analysis?**	**(11) Post-randomization exclusions?**	**(12) Quality Rating**
Hass et al., 1989 (12), North America, TASS (good)	3% ticlopidine (n=46) and 2% assigned to the ASA group, (n=38)	yes	Yes	Good
Juergens C et al., 2004 (23), Australia (poor)	No	Yes	No	poor
Rupprecht et al., 1998 (31), Germany (poor)	No	No	Unable to determine	poor

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Mueller C. et al., 2003 (27), Germany and Switzerland	Number screened not reported/number eligible not reported/700 enrolled	unsuccessful stent placement was all that was reported but would suspect that the exclusions study would be similar to Mueller 2000 et al. study	None	Not reported
Atmaca et al., 2002 (25), Ankara, Turkey	168 screened, number eligible not reported/ 158 enrolled	unstable angina, AMI within 2 wks, 12 lead resting ECK with R or L BBB, paced rhythm or complete atrioventricular block, CABG within 2 wks, renal dysfunction, pericardial disease, cardiomyopathy, recent myocarditis. Pts who received a stent as a bailout indication, and pts who were given tirofian during the procedure	None	No (unsure)
Taniuchi et al., 2001 (30), USA	1367 screened/Number eligible not reported/number enrolled not reported/1016 randomized	1. prior intolerance to ASA, T or C, 2. a comorbidity with expected survival of < 6 months and 3. prior enrollment in a separate research protocol	None	Yes
Mueller C. et al., 2000 (26), Germany	793 screened/Number eligible not reported/700 enrolled (699 completed clinical f/u)	Cardiogenic shock, mechanical ventilation; known allergy to ASA, T, or C; long-treatment with T, C, or warfarin; and stenting intended primarily as a bridge to CABG	None	No

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Leon et al., 1998 (32), USA	1965 screened;1653 eligible; 1653 enrolled. (Of the 312 enrolled in the parallel registry-298 were eligible)	unsuccessful stent placement -they were then enrolled in a prospective registry trial. Presence of additional stenosis within the target vessel; recent (within 7 days before enrollment) AMI; known contraindications to the use of ASA, T or warfarin; a hx of bleeding diathesis; current treatment with abciximab; and planned angioplasty of another lesion within 30 days after enrollment.	Not-applicable	Yes
Bertrand et al., 2000 (29), Europe CLASSICS	Number screened not reported/1021 eligible/1020 enrolled	1. stenting procedure involving ≥stents or >1 vessel, involving the left main coronary artery or a major bifurcation, or involving vein grafts; primary angioplasty for ongoing MI with documented ST elevation and/or CPK-MP levels >2XULN and CPK MB levels greater than normal; persistent objective ischemia determined by 12 lead ECG between stenting and randomization; administration of oral anticoagulants. GP 2b/3A receptor antagonists and other antiplatelet agents, except for ASA within 1month before randomization; administration of thrombolytics 2 wks before randomization; need for anticoagulants, thrombolytic agents, or GP 2b/3a receptor antagonists after the procedure; PTCA, CABG within 2 months before the procedure; hx of allergy or intolerance or contraindication to ASA< T, or C.	None	Yes-pt had hx of allergy or intolerance/contraindication to ASA, T or C--excluded

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Hall et al., 1996 (28), Milan, Italy and Tokyo, Japan	Number screened 358 (stent deployment)/Number eligible not reported/ 226 enrolled	allergic to ASA, taking T or other non-aspirin antiplatelet agents before the procedure, or required warfarin for other medical reasons were excluded. Pt with suboptimal results at the end of the stent procedure were excluded	No	Yes
Diener et al., 2004 (11), 28 countries including multiple ones in Europe, USA, Spain	Number screened not reported/number eligible not reported/ 7599 enrolled.	are younger than 40 years; severe comorbid conditions; increased risk of bleeding (clinical evidence of severe hepatic insufficiency, current peptic ulceration, history of systemic bleeding, or other history of bleeding diathesis or coagulopathy); scheduled for major surgery or vascular surgery; and contraindications for ASA or clopidogrel.	None	No

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Gorelick et al., 2003 (41), 62 academic and community hospitals in USA	Number screened not reported/number eligible not reported/ 1809 enrolled. (902 in Ticlopidine were included in analysis vs. 907 in the ASA group)	TIA, subarachnoid hemorrhage, cardiac source embolism, iatrogenic or nonatherosclerotic strokes, postoperative stroke occurring within 30 days of operation, or carotid endarterectomy as primary treatment measure for entry cerebral infarct; mean arterial blood pressure >130 mmHg on 3 consecutive days; modified Barthel index <10; hx of dementia or neurodegenerative disease; severe comorbid condition (eg cancer) judged to limit survival during 2 yr f/u; enrollment in another clinical trial; allergy or sensitivity to study drugs; woman of childbearing potential; GI bleeding; bleeding diathesis, or plt or other hematologic abnormality curently active or clinically active in the past year; hematuria or positve tool guaiac test related to mj bleeding source; and prolonged prothrombin time or partial thromboplastin time. BUN >40mg/dL, serum Cr >2.0mg/dL, thrombocytopenia or neutropenia, LFT >=2X ULN, a.fib, cardiac sources of embolism requiring warfarin therapy, large artery carotid occlusive disease treated by CEA, which would serve to increase the likelihood of enrolling lacunar infarction	None	Undetermined
CAPRIE Steering Committee, 1996 (13), International	Number screened not reported/number eligible not reported/ 19185 patients enrolled	Age <21 years; severe cerebral deficit likely to lead to pt being bedridden or demented, carotid endartectomy after qualifying stroke; qualifying stroke induced by carotid endarterectomy or angiography; pt unlikely to be discharged alive after qualifiying event; severe co-morbidity likely to limit pt's life expectancy to <3 y, uncontrolled hypertension, scheduled for major surgery, contraindications to study drugs: severe renal or hepatic insufficiency, haemostatic disorder or systemic bleeding, hx of haemostatic disorder of systemic bleeding, hx of thrombocytopenia or neutropenia, hx of drug-induced haematologic or hepatic abnormalities, known to have abnormal WBC, differential, or platelet count, anticipated requirement for long-term anticoagulants, non-study antiplatelet drugs or NSAIDs affecting plt. function; Hx of ASA sensitivity; Women of childbearing age not using reliable contraception, currently receiving investigation drug, previously entered in other clopidogrel studies, geographic or other factors making study partipciation impractical.	use of anticoagulants or antiplatelet drugs were discontinued before randomization and thrombolytic treatment should not have been received within the previous 48 hours.	No

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Diener et al., 1996 (10), multicenter-59 sites in 13 countries between 2/89 and 3/95	see above	See above	None	Undetermined
ESPS-2 Authors, 1997 (38), multicenter-59 sites in 13 countries	Number screened not reported/number eligible not reported/ 6602 enrolled	Not specified in this article	None	Undetermined
Juergens C et al., 2004 (23), single center, Australia	Number screened not reported/number eligible not reported/307 enrolled	Cardiogenic shock, unsuccessful stent deployment; known allergy to ASA, ticlopidine, or clopidogrel; recurrent treatment with C or T and need to anticoagulants after the procedure .	None	No
Mehta et al., 2001 (8), International, (PCI-CURE)(good)	Number screened not reported /number eligible (had PCI) 2658/2658 enrolled	contraindications to antithrombotic/antiplatelet therapy, those at high risk of bleeding, New York Heart Association Class IV heart failure, ongoing long-term need for oral anticoagulants, undergone PCI (PTCA/stent) or coronary-artery bypass grafting in the previous 3 months prior to randomization, or received a glycoprotein 2b/3a inhibitor fewer than 3 days before randomization.	No	No

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Piamsomboon et al., 2001 (22), Bangkok, Thailand, single center (poor)	Number screened not reported/number eligible not reported/ 68 patients enrolled	contraindication to antiplatelet stents, left main coronary artery disease, hemostatic disorder or systemic bleeding, history of thrombocytopenia or neutropenia, presence of abnormal white blood cell, differential or platelet count, requirement of long-term anticoagulant or non-steroidal anti-inflammatory drugs, childbearing age women, and severe hepatic or renal dysfunction	No	No
Cure Investigators et al., 2001 (6), International	Number screened not reported/number eligible not reported/ number enrolled not reported/12,562randomized	contraindications to antithrombotic/antiplatelet therapy, those at high risk of bleeding, New York Heart Association Class IV heart failure, ongoing long-term need for oral anticoagulants, undergone PCI (PTCA/stent) or coronary-artery bypass grafting in the previous 3 months or had received IV GYP 2b/3a receptor inhibitors in the previous 3 days	None	No
Fiotti et al., 2003 (46), Italy, single-centered (fair-poor)	Number screened not reported; Number eligible not reported/numbers enrolled 223/numbers randomized 223. For the match control group: 8% of all putative controls contacted refused to enter into study. 446 matched controls living in the same area was enrolled during the same time period	Symptoms did not meet WHO criteria for intermittent claudication i.e. leg pain on walking disappearing in less than 10 min on standing, and ankle/brachial pressure index less than 0.80 in either leg at rest (two assessment on separate days). From the match group- same family name of on of the pts were excluded.	No	Not reported
Steinhuble et al., 2002 (9), North America, CREDO (good)	17898 screened/2116 eligible/2116 enrolled/2116 randomized	contraindications to antithrombotic/antiplatelet therapy; greater than 50% stenosis of the left main coronary artery; failed coronary intervention in the previous 2 weeks; coronary anatomy not amenable to stent placement; persistent ST elevation within 24 hours prior to randomization; planned staged interventional procedure; and administration of the following medications prior to randomization; GP 2b/3a inhibitor within 7 days, clopidogrel within 10 days, or thrombolytics within 24 hours.	No	No

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity			
Author, Year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**
Hass et al., 1989 (12), North America, TASS (good)	8814/3069/3069/3069	Patient less than 40 years of age, women with childbearing potential, symptoms were due to migraine, carcinogenic embolism, or hematological disorders were ineligible as were those with a history of peptic ulcer disease, upper GI bleeding, ,or life-threatening diseases such s cancer. Those with previous hypersensitivity or intolerance to ASA and those with a need for the continued use of ASA or anticoagulants.	None	No
Juergens C et al., 2004 (23), Australia (poor)	307/307/307/307	Cardiogen shock; unsuccessful stent deployment; known allergy to aspirin, ticlopidine, or clopidogrel; recent treatment with clopidogrel or ticlopidine; and need for anticoagulants after the procedure	None	No
Rupprecht et al., 1998 (31), Germany (poor)	not reported/not reported/not reported/61	bleeding disorders, contraindications to treatment with aspirin and/or ticlopidine, abnormal blood cell count, childbearing potential, acute MI, depressed LV fx, renal insufficiency, or an indication for oral anticoagulation	No	No

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity		
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Mueller C. et al., 2003 (27), Germany and Switzerland	Yes-although C was initiated without a LD	Not reported	The study is the first presentation of extended f/u data from a randomized trial. The mean f/u as 28 months in the T group and 27 months in the C group
Atmaca et al., 2002 (25), Ankara, Turkey	Yes-T 500mg every day + 300mg ASA d	Not reported	No10/168 enrolled were excluded for receiving a stent as a bailout indication and tirofiban treatment during the procedure
Taniuchi et al., 2001 (30), USA	Yes	Sanofi/Bristol-Meyers Squibb	Yes-broad population included AMI and those with adjunctive 2b/3A inhibitors. States that the population more representative of pts receiving intracoronary stents in the US. Diabetics constituted 29% of the population vs. 21-23 in Muller study(2000) and 10-12 in CLASSICS.
Mueller C. et al., 2000 (26), Germany	Yes in regards to T but note: C was used without a LD	Not reported	No-the study was not performed to show a statistical significant difference in cardiac events. However, there was a higher TSO incidence in pts assigned to C group.

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity		
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Leon et al., 1998 (32), USA	Yes	Supported by a grant from Cordis, a Johnson and Johnson Company	high rate of stent thrombosis in group assigned to ASA alone contradicts previous reports stating that it was similar to A + T; death rate is low which may be contribute to the fact that there were differences in selection factors used or improved diagnosis and tx strategies for stent thrombosis. It did have a high percentage of Q wave which indicates that the clinical consequences of stent thrombosis remain severe. Lower incidence of stent thrombosis in ASA and T group is offset by sl but SS increased risk of hemorrhagic and vascular surgical complications. Although the incidence of hemorrhagic complications in the group assigned to ASA and W was lower than previous studies which might indicate that femoral-artery puncture and sheath-removal techniques have improved over the years.
Bertrand et al., 2000 (29), Europe CLASSICS	Yes	Funded by Sanofi and BMS	Yes-compare the relative safety of C with and without LD compared with T + ASA in pt who had undergoing successful intracoronary stenting. Secondary objective--evaluate the incidence occurrence of cardiac events during the period of study drug administration. Population was low-risk--pts tat had successful stent. This study was underpowered to show efficacy differences

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity		
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Hall et al., 1996 (28), Milan, Italy and Tokyo, Japan	Yes	Not reported	relevant to some extent, however pts had to have a successful intravascular US-guided stenting in order to be randomized--pt selection bias but eliminates some of the issue that stent thrombosis was due to a mechanical reason vs. pharmacological. Unclear whether a population that stent was performed in pt for emergency reasons or those with small vessels or long vessels would be different. A larger cohort of pt would be necessary for assessment of any significant difference between the antiplatelet regimens due to the low incidence of thrombosis events or other clinical end points between the two poststent antiplatelet regimens. There was a sl imbalance in the # of pts in each group (ASA- 103 and T-123) owing to premature termination of the study before the expected target of 450 pt after the 3 deaths in the ASA group.
Diener et al., 2004 (11), 28 countries including multiple ones in Europe, USA, Spain	yes	MATCH steering committee had overall responsibility for the implementation of the trial. Sanofi-Synthelabo contracted Parexel International (Paris, France) to undertake site monitoring and data management. Sanofi-Synthelabo provided input into the study through 3 of its employees, who represented the sponsor on the steering committee (representing only 1 vote of 10) and paid study-related expenses to the other members of the committee. The data safety monitoring board had full access to the database throughout the trial. The steering committee had full access after closure of the database, and final key analyses were done separately and in parallel by sponsor and by statisticians who worked independently from sponsor	high-risk patients (majority of pts already on ASA) with mainly lacunar strokes included were included

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity		
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Gorelick et al., 2003 (41), 62 academic and community hospitals in USA	yes	None	All African American pts-at the time the study was developed there was uncertainty about the referred ASA dose for recurrent stroke prevention
CAPRIE Steering Committee, 1996 (13), International	Yes	Study was funded by Sanofi and Bristol-Myers Squibb	first study of an antiplatelet drug to include pts from the clinical subgroups of ischemic cerebrovasclar, cardiac and PAD..Study was powered to detect a realistic treatment effect in the whole study cohort but not in each of the 3 clinical subgroups.

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity		
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Diener et al., 1996 (10), multicenter-59 sites in 13 countries between 2/89 and 3/95	Yes	supported by a grant from Boehringer Ingelheim	
ESPS-2 Authors, 1997 (38), multicenter-59 sites in 13 countries	Yes	Not reported	# treatment interruptions: Placebo group n= 1649: 127 (adverse events), 148 (other medical reason), 81 (non-medical reason), 4 unknown reason, Lost to follow-up or endpoint 358 (21.7%) ; ASA group n= 1649: 141 (adverse events, 149 (other medical reason), 72 (non-medical reason), 4 unknown reason, Lost to follow-up or endpoint 302 (18.3%); DP group n= 1654: 249 (adverse events), 136 (other medical reason), 95 (non-medical reason); 5 unknown reason) Lost to follow-up or endpoints 279 (16.9%); DP-ASA n= 1650: 262 adverse events, 136 (other medical reason). 79 (non-medical reason), 2 unknown reason, Lost to follow-up or endpoints 248 (15%)
Juergens C et al., 2004 (23), single center, Australia	Yes-except for the low LD of clopidogrel	Not reported	not randomized, open-labeled, single centered, ? Allocation method, use of GP 2B/3An varied not only the agents but the frequency. LD of clopidogrel was 150mg instead of 300mg
Mehta et al., 2001 (8), International, (PCI-CURE)(good)	Yes	Supported by a research grant from Sanofi-Synthelabo and Bristol-Myers-Squibb	Patients were consider "moderate risk" group of patients with ACS--may not be generalizable to high-risk group of patients

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity		
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Piamsomboon et al., 2001 (22), Bangkok, Thailand, single center (poor)	No-would not use as high of dose of ASA any longer	Not reported	Small sample size limits generalizability of results; dose of ASA is no longer being utilized; 4 different types of stent used
Cure Investigators et al., 2001 (6), International	Yes	Supported by Sanofi-Synthelabo and Bristol-Myers Squibb	Patients were consider "moderate risk" group of patients with ACS--may not be generalizable to high-risk group of patients
Fiotti et al., 2003 (46), Italy, single-centered (fair-poor)	No	Not reported	No-pts could select drug therapy, population was from northern Italy-perhaps not generalizable; medications taken by match control group was not stated
Steinhuble et al., 2002 (9), North America, CREDO (good)	Yes	supported from Bristo-Meyers Squibb/Sanofi-Synthelabo partnership.	high proportion of pts discontinued study med prior to the completion of the full year of follow-up so that the risk reduction associated with long-term clopidogrel may be underestimated. Unknown whether pretreatment therapy contributed any to the benefit of the long-term therapy. (63% in clopidogrel group and 61% of control patients completed 1 year). (45% clopidogrel and placebo patients DC study drug after PCI)

Evidence Table A2. Quality Assessment for Controlled Trials

	External Validity		
Author, Year Country	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Hass et al., 1989 (12), North America, TASS (good)	No-standard of care would no longer be 1300mg daily	Supported by Syntex Research	yes
Juergens C et al., 2004 (23), Australia (poor)	N0-ASA dose was 300mg the day before and then a minimum of 100mg per day after that. Clopidogrel 150 was given after the procedure. Both ticlopidine and clopidogrel was given x 14 days	Not reported	No-treatment arms are not utilized in practice any longer
Rupprecht et al., 1998 (31), Germany (poor)	No-Asa dose with ticlopidine is higher (300mg) than what would be used in practice	Not reported	No-outcomes were reported was primarily a comparison of the antiplatelet effects .

Evidence Table A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
Mueller et al., 2003 (27)	Yes	Yes	Yes-Primary endpoint-CV death during the entire f/u period--(defined as any death for which there was no clearly documented non-cardiac cause. Secondary end point-composite of cardiac death and MI (typical CP at rest followed by an increase in CK and CK-MB beyond 2X ULN and 5X ULN after CABG, new Q waves. No bleeding monitoring were included
Atmaca et al., 2003 (25)	Yes	yes-6%	Yes-procedure related MMI and major clinical events (death, AMI, and PTCA or bypass surgery). Also, major or minor bleeding complications during hospitalization period--not defined. Deaths-cardiac origin if associated with CHF, AMI or sudden cardiac death (<1 hr after symptom onset). AMI= new Q wave or the ST elevation lasting more than 1 day and the development of T wave change; new specific ST segment elevation or depression ≥0.1 mV; and increase in CK, CK-MB activity
Taniuchi et al., 2001 (30)	Yes	Yes	Yes
Muller et al., 2000 (26)	Yes	Yes	Yes
Moussa et al., 1999 (24)	Yes	Not clear-1.1% (16 pts) in TA group (n=1406) vs. 0.7% (2 pts) in CA group (n=283) were lost to follow-up	No

Evidence Table A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
Leon et al., 1998 (32)	Yes	Yes	Yes
Bertrand et al., 2000 (29)	Yes	Yes	Yes
Hall et al., 1996 (28)	Yes	Yes	Yes
Diener et al., 2004 (11)	Yes	Yes	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
Gorelick et al., 2003 (41)	Yes	No the drop-out rate or voluntary withdrawal were 15.2% in Ticlopidine tx group and 13.3% for those receiving ASA	Yes
CAPRIE Investigators et al., 1996 (13)	Yes	Yes	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
ESPS-2 authors, 1997 (38)	yes	No	yes
Juergens et al., 2004 (23)	Yes	Yes	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
Quilliam et al., 2001 (64)	No-case-control design	N/A-case control design	No
Rupprecht et al., 1998 (31)	Yes	Yes	Yes-although those that were prespecified were not outcomes of interest to this report i.e. platelet Aggregation Studies, Flow Cytometric Analysis, Platelet Count
Mehta et al., 2001(8) (PCI-CURE)	Yes	Yes	Yes
Piamsomboon et al., 2001 (22)	Yes	Yes	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
CURE Investigators et al., 2001 (6)	Yes	Yes	Yes
Fiotti et al., 2003 (46)	No-match case control	Yes	Yes
Steinhuble et al., 2002 (9) (CREDO)	Yes	Yes	yes

Evidence Table A3. Adverse Event Quality Table

Author Year	1) Non-biased selection?	2) Low overall loss to follow-up?	3) Adverse events pre-specified and defined?
Hass et al., 1989 (12), North America	yes	No-higher than other studies but less than 5%	yes

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
Mueller et al., 2003 (27)	Yes-f/u visits at "our" institution at 6 months and whenever clinically indicated thereafter. All pts were contacted by questionnaire to assess vital and functional status as well as MACE 2 years after enrollment of the last pt. If pt did not return a signed questionnaire or any uncertainties remained, a MD interviewed the pts and their family MD over the phone. Information from contingent hospital re-admission records or provided by referring MD or by the outpt clinic was reviewed.	No	Yes
Atmaca et al., 2003 (25)	No	No-were blinded but ascertainment techniques specifically to address bleeding complications were not included	Yes
Taniuchi et al., 2001 (30)	No	No-	Yes
Muller et al., 2000 (26)	Yes	no	Yes
Moussa et al., 1999 (24)	No	No--pts were instructed to f/u with their referring MD in 2 wks for clinical assessment and blood count analysis (all different). NP performed telephonic f/u eval at 1 month on an ongoing basis. A quantitative angiography was done pre and post procedure	No-Quantitative angiography- the minimum lumen diameter in mm was 0.90 ± 0.45 vs. 0.84 ± 0.47 in the TA group, p= 0.02 preprocedure but postprocedure the diameter was similar, p=1.

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
Leon et al., 1998 (32)	Yes	Yes	Yes
Bertrand et al., 2000 (29)	No	Unsure-pts and assessors were blinded but ascertainment techniques were not stated	Yes
Hall et al., 1996 (28)	Yes	Yes-Coronary angiograms were analyzed without knowledge of the intravascular ultrasound data by experienced angiographers not involved in the stenting procedure.	Yes
Diener et al., 2004 (11)	Yes	Yes	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
Gorelick et al., 2003 (41)	yes	yes	Yes
CAPRIE Investigators et al., 1996 (13)	Yes	Yes	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
ESPS-2 authors, 1997 (38)	yes	Yes	Yes
Juergens et al., 2004 (23)	Yes	No	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
Quilliam et al., 2001 (64)	No	No	Yes
Rupprecht et al., 1998 (31)	Yes	Unsure	Yes
Mehta et al., 2001(8) (PCI-CURE)	No	Yes although pts/providers were not during the open-label section of the study although there was central adjudication done by a committee of clinicians who were blinded to treatment allocation	Yes
Piamsomboon et al., 2001 (22)	Yes	Unsure-randomized pts unclear whether patients and assessors were blinded to intervention, and whether ascertainment techniques were valid	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
CURE Investigators et al., 2001 (6)	Yes	Yes	Yes
Fiotti et al., 2003 (46)	Yes	No	Yes
Steinhuble et al., 2002 (9) (CREDO)	Yes	Yes although pts/providers were not during the open-label section of the study although there was central adjudication done by a committee of clinicians who were blinded to treatment allocation	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	4) Ascertainment techniques adequately described?	5) Non-biased and adequate ascertainment methods	6) Statistical analysis of potential confounders?
Hass et al., 1989 (12), North America	yes-pts were evaluated one month after randomization and then 4 month interval throughout the trial.	Yes	Yes

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8)Overall adverse event assessment quality
Mueller et al., 2003 (27)	Yes	Fair/poor-not blinded, multiple providers, questionnaires used but data not reported
Atmaca et al., 2003 (25)	Yes-study was intended to evaluate during hospitalization	fair-ascertainment methods were not detailed
Taniuchi et al., 2001 (30)	Yes-for the tolerability portion of the study. i.e. drugs given x 2 wks which was the length of time for primary safety end point. Secondary cardiac end points were documented throughout a 30 day after stent implementation	fair-done at single-site, open-label administration of drugs, with twice dosing of T and single dosing of C
Muller et al., 2000 (26)	yes	fair-unblinded
Moussa et al., 1999 (24)	Yes- BUT incidence of stent thrombosis, MACE and drug SE was reported at 1 month f/u but T was given for only 2 weeks	Poor--not randomized, pts were assessed by their own referring MD in 2 wks, study was a chronologically consecutive manner (all the pts btw 96-98 received T and those btw Mar. 98 and Jun. 98 received C. The incidence of stent thrombosis with antiplatelet therapy is low (1.5% TA group vs. 1.4% in CA group, p = NS), a large randomized trial is needed to establish validity of these data

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8)Overall adverse event assessment quality
Leon et al., 1998 (32)	Yes	good
Bertrand et al., 2000 (29)	Yes	good
Hall et al., 1996 (28)	Yes	Poor-unblinded randomized-open label, not same qty of pts in each group;
Diener et al., 2004 (11)	Yes	good

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8)Overall adverse event assessment quality
Gorelick et al., 2003 (41)	Yes	fair/good-high drop out rate
CAPRIE Investigators et al., 1996 (13)	Yes	good

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8)Overall adverse event assessment quality
ESPS-2 authors, 1997 (38)	Yes	fair/good-high drop out rate
Juergens et al., 2004 (23)	Yes	Poor

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8)Overall adverse event assessment quality
Quilliam et al., 2001 (64)	yes	Poor--not randomized but case-control with data derived from SAGE-Systematic Assessment of Geriatric Drug use Via Epidemiology from 1992-1997. Studied the likelihood of hospitalization for bleeding among elderly nursing home stroke survivors from 5 states.Hospitalization claims for outcome identification were used--possibly missing less severe cases for inclusion. Potential for misclassification of bleeds i.e. GI bleeds may range from minor to life threatening. No information on the actual indication for use of these agents and presumed that they are being used for secondary stroke prevention. By design, residents were excluded with a known hospitalization for bleeding from the sample of potential controls. The first recorded hospitalization for a bleeding event within the sudy was used among the cases as the event of interest.....possible that pts were hospitalizaed for bleeding before the claims data were available
Rupprecht et al., 1998 (31)	No-lab investigations were performed on days 1,7 and day 14 after stent implantation although therapy was x 4 weeks	
Mehta et al., 2001(8) (PCI-CURE)	Yes	good
Piamsomboon et al., 2001 (22)	yes	Poor-ascertainment methods were not detailed, randomization was done by "research nurse" with no other details, questionable whether patients/providers were blinded, multiple providers were involved

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8)Overall adverse event assessment quality
CURE Investigators et al., 2001 (6)	Yes	Good
Fiotti et al., 2003 (46)	Yes	Fair/poor-pt selected own therapy; match-control for age and gender and not disease states; used Regional Health Service Data Base to select controls
Steinhuble et al., 2002 (9) (CREDO)	Yes	good

Evidence Table A3. Adverse Event Quality Table

Author Year	7) Adequate duration of follow-up?	8)Overall adverse event assessment quality
Hass et al., 1989 (12), North America	Yes	good

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
Mueller et al., 2003 (27)	no adverse events reported
Atmaca et al., 2003 (25)	Ticlopidine vs Clopidogrel Bleeding: 0.0% (0/75) vs 0.0% (0/83)
Taniuchi et al., 2001 (30)	
Muller et al., 2000 (26)	Ticlopidine + Aspirin vs Clopidogrel + Aspirin Hemorrhagic complications: 0.9% (3/345) vs 0.6% (2/355) Neutropenia or thrombocytopenia: 0.9% (3/345) vs 0% (0/355) Vascular surgical complications: 1.7% (6/345) vs 2% (7/355)
Moussa et al., 1999 (24)	Ticlopidine + Aspirin vs Clopidogrel + Aspirin Diarrhea: 4.4% (61/1390) vs 3.2% (5/281) Neutropenia: 0.3% (4/1390) vs 0.0% (0/281) Rash: 5.9% (82/1390) vs 2.1% (6/281)

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
Leon et al., 1998 (32)	Ticlopidine + Aspirin vs Aspirin Cerebrovascular: 0.0% (0/546) vs 0.4% (2/557) Hemorrhagic complications: 5.5% (30/546) vs 1.8% (10/557) Neutropenia or thrombocytopenia: 0.5% (3/546) vs0.2% (1/557) Vascular surgical complications: 2.0% (11/546) vs 4.0% (2/557)
Bertrand et al., 2000 (29)	Ticlopidine vs Clopidogrel 75mg vs Clopidogrel 300/75mg Allergy: 1.2**%** (4/340) vs 0.00% (0/335) vs 0.00% (0/345) Gastrointestinal disorder: 2.6% (9/340) vs 2.4% (8/335) vs 0.3% (1/345) Major peripheral or bleeding complication: 1.2% (4/340) vs 1.2% (4/335) vs 1.5% (5/345) Neutropenia <1.5 x 10to9/L: 0.3% (1/340) vs 0.00% (0/335) vs 0.00% (0/345) Skin disorder: 2.6% (9/340) vs 0.9% (3/335) vs 0.6% (2/345) Thrombocytopenia 70-100x10to0/L: 0.3% (1/340) vs 0.00% (0/335) vs 0.00% (0/345)
Hall et al., 1996 (28)	Ticlopidine + Aspirin vs Aspirin Vascular complication: 0% (0/123) vs 1% (1/103) Leukopenia: 0.8% (1/123) vs 0.0% (0/103) Skin rash: 1.6% (2/123) vs 0.0% (0/123)
Diener et al., 2004 (11)	Clopidogrel + Aspirin vs Clopidogrel + Placebo Life-threatening bleeding: 2.6% (96/3759) vs 1.3% (49/3781) Fatal-bleeding: <1.0% (16/3759) vs <1.0% (11/3781) Non-fatal bleeding: 1.0% (38/3781) vs 2.0% (81/3759) Symptomatic intracranial: 1.0% (25/3781) vs 1.0% (40/3759) Primary intracranial haemorrhage: 1.0% (32/3759) vs <1.0% (17/3781) Major bleeding: 1.9% (73/3759) vs 0.6% (22/3781)

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
Gorelick et al., 2003 (41)	Ticlopidine vs Aspirin Cardiovascular system: 7.3% (66/902) vs 8.4% (76/907) Diarrhea: 0.3% (3/902) vs 0.2% (2/907) Digestive system: 4.2% (38/902) vs 4.7% (43/907) Endocrine system: 1.2% (11/902) vs 1.1% (10/907) Hemic & lymphatic system: 4.2% (38/902) vs 3.2% (29/907) Major GI tract hemorrhage: 0.4% (4/902) vs 2.2% (20/907) Musculoskeletal system: 1.9% (17/902) vs 1.2% (11/907) Nervous system: 7.3% (66/902) vs 6.6% (60/907) Neutropenia: 3.4% (31/902) vs 0.9% (8/907) Other bleeding : 0.7% (6/902) vs 1.2% (11/907) Psychiatric system: 1.1% (10/902) vs 0.6% (5/907) Respiratory system: 4.2% (38/902) vs 4.1% (37/907) Skin & appendages: 1.7% (15/902) vs 1.7% (15/907) Special senses: 0.3% (3/902) vs 0.7% (6/907) Thrombocytopenia: 0.3% (3/902) vs 0.2% (2/907) Urogenital system: 2.7% (24/902) vs 1.9% (17/907)
CAPRIE Investigators et al., 1996 (13)	Clopidogrel vs Aspirin Abnormal liver function: 3.0% (285/9599) vs 3.2% (302/9586) Any bleeding disorder: 9.3% (890/9599) vs 9.3% (890/9586) Diarrhea: 4.5% (428/9599) vs 3.4% (322/9586) GI haemorrhage: 2.0% (191/9599) vs 2.7% (255/9586) Indigestion/nausea/vomiting: 15.0% (1441/9599) vs 17.6% (1686/9586) Intracranial haemorrhage: 0.4% (34/9599) vs 0.5% (47/9586) Rash: 6.0% (578/9599) vs 4.6% (442/9586)

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
ESPS-2 authors, 1997 (38)	Dipyridamole vs Dipyridamole + Aspirin vs Aspirin vs Placebo GI event: 30.5% (505/1654) vs 32.8% (541/1650) vs 30.4% (502/1649) vs 13.3% (219/1649) Nausea: 14.8% (245/1654) vs 15.4% (254/1650) vs 12.4% (204/1649) vs 13.7% (226/1649) Dyspepsia: 16.6% (274/1654) vs 17.6% (290/1650) vs 17.2% (283/1649) vs 16.1% (266/1649) Vomiting: 7.2% (119/1654) vs 8.1% (133/1650) vs 5.6% (93/1649) vs 6.6% (109/1649) Gastric pain: 14.5% (240/1654) vs 16.6% (274/1650) vs 14.7% (242/1649) vs 13.3% (219/1649) Diarrhea: 15.4% (254/1654) vs 12.1% (199/1650) vs 6.6% (109/1649) vs 9.3% (154/1649) Headache: 37.2% (615/1654) vs 38.2% (630/1650) vs 33.1% (546/1649) vs 32.4% (534/1649) Bleeding any site (total): 4.7% (77/1654) vs 8.7% (144/1650) vs 8.2% (135/1649) vs 4.5% (74/1649) Dizziness: 30.1% (498/1654) vs 29.5% (486/1650) vs 29.2% (481/1649) vs 30.9% (509/1649)
Juergens et al., 2004 (23)	Ticlopidine + Aspirin vs Clopidogrel + Aspirin Any non-cardiac event: 3.9% (6/153) vs 1.9% (3/154) Bleeding: 0.7% (1/153) vs 0.6% (1/154) Dermatological:1.3% (2/153) vs 0% (0/154) Gastrointestinal: 1.3% (2/153) vs 0.0% (0/154) Haemorrhageic complications: 0.0% (0/153) vs 0.6% (1/154) Vascular complication: 1.3% (2/153) vs 1.3% (2/154) 16 pts in TA group (1.1%) and 2 pts in the CA group (0.7%) were lost to f/u. 46 pt (3.3%) in the TA group and 8 pts (2.8%) in the CA group p=0.85) DC the study drug early for reasons other than the occurrence of an outcome events. Reasons for stopping T: rash in 30 pts; Diarrhea in 6 pts; rash and diarrhea in 5 pts, neutropenia in 4 pts and noncompliance in 1 pt. Reasons for DC C were rash in 4 pts, diarrhea in 3 pts and noncompliance in 1 pt. The incidence of stent thrombosis, cardiac events, and med side effects at 1 month f/u was reported for 1671pts

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
Quilliam et al., 2001 (64)	no adverse events reported
Rupprecht et al., 1998 (31)	Ticlopidine vs Ticlopidine + Aspirin vs Aspirin Major bleeding: 0% (0/20) vs 0% (0/21) vs 5.0% (1/20)
Mehta et al., 2001(8) (PCI-CURE)	Clopidogrel vs Placebo Major bleeding: 2.7% (36/1313) vs 2.5% (33/1345) Life-threatening bleeding: 1.2% (16/1313) vs 1.3% (18/1345) Non-life-threatening bleeding: 1.5% (20/1313) vs 1.1% (15/1345) Minor bleeding: 3.5% (46/1313) vs 2.1% (28/1345) Blood transfusions of 2 or more units: 2.1% (28/1313) vs 2.0% (27/1345)
Piamsomboon et al., 2001 (22)	Ticlopidine + Aspirin vs Clopidogrel + Aspirin Major bleeding: 3.2% (1/31) vs 5.4% (2/37) Minor bleeding: 0.0% (0/31) vs 5.4% (2/37) Rash: 3.2% (1/31) vs 0% (0.0/37)

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
CURE Investigators et al., 2001 (6)	Clopidogrel vs Placebo Major bleeding: 3.7% (231/6259) vs 2.7% (169/6303) Life-threatening bleeding: 2.2% (135/6259) vs 1.8% (112/6303) Transfusion of 2 or more units of blood: 2.8% (177/6259) vs 2.2% (137/6303) Early major bleeding: 2.0% (125/6259) vs 1.5% (95/6303) Late major bleeding: 1.7% (106/6259) vs 1.1% (69/6303) Major bleeding after CABG: 1.3% (81/6259) vs 1.1% (69/6303) Minor bleeding: 5.1% (322/6259) vs 2.4% (153/6303) Vascular complication: 1.3% (2/154) vs 1.3% (2/153) Thrombocytopenia: 0.4% (26/6259) vs 0.4% (28/6303) Neutropenia: 0.1% (8/6259) vs 0.1% (5/6303)
Fiotti et al., 2003 (46)	Ticlopidine vs Aspirin Minor bleeding: 6% (6/92) vs 1.5% (20/131) Upper GI discomfort: 15.2% (14/92) vs 6.1% (8/131)
Steinhuble et al., 2002 (9) (CREDO)	Clopidogrel vs Placebo Major bleeding: 8.8% (93/1053) vs 6.7% (71/1063) Non-procedural major bleeding: 1.2% (13/1053) vs 0.8% (8/1063) Procedural major bleeding: 7.7% (81/1053) vs 5.9% (63/1063) Major bleeding from CABG: 6.0% (63/1053) vs 5.2% (55/1063) Major bleeding from non-CABG: 1.7% (18/1053) vs 0.8% (8/1063) Minor bleeding: 5.3% (56/1053) vs 5.6% (59/1063) Non-procedural minor bleeding: 5.3% (56/1053) vs 5.6% (59/1063) Procedural minor bleeding:4.7% (50/1053) vs 4.9% (52/1063) Minor bleeding from CABG: 2.3% (24/1053) vs 2.8% (30/1063) Minor bleeding from non-CABG: 2.5% (26/1053) vs 2.1% (22/1063)

Evidence Table A3. Adverse Event Quality Table

Author Year	Adverse Events Results
Hass et al., 1989 (12), North America	Ticlopidine vs Aspirin Diarrhea: 20.4% (310/1518) vs 9.8% (150/1527) Dyspepsia: 12.6% (191/1518) vs 13.8% (210/1527) Nausea: 11.1% (169/1518) vs 10.2% (156/1527) Gastrointestinal pain: 7.2% (110/1518) vs 10.0% (153/1527) Gastritis: 0.9% (13/1518) vs 1.7% (26/1527) Gastrointestinal hemorrhage: 0.5% (7/1518) vs 1.4% (21/1527) Peptic ulcer: 0.8% (12/1518) vs 2.9% (45/1527) Rash: 11.9% (180/1518) vs 5.2% (80/1527) Urticaria: 2.0% (30/1518) vs 0.3% (5/1527) All hemorrhagic: 9.0% (137/1518) vs 10.0% (152/1527) Severe neutropenia: 0.9% (13/1518) vs 0.0% (0/1527)

Evidence Table A4. Systematic Reviews

Author Year	Aims	Time period covered
Casella et al. 2003 (34)	compare the clinical efficacy of C + ASA vs. T+ ASA (standard therapy) after coronary stenting via formal meta-analysis	studies/abstracts included up to Dec. 2001
Robless et al. 2001 (52)	To provide evidence-based recommendations on the use of antiplatelet treatment for the prevention of CV events and stroke in PVD pts.	Databases used Medline 1/66-1/99; Embase 1/80-1/99; register of trials held by the APTC; Cochrane Controlled Trials Register; Proceeding from vascular surgical society mgt, pharmaceutical companies that market antiplatelet agents (T C)
Bhatt et al. 2002 (33)	determine whether clopidogrel plus ASA is at least as efficacious as ticlopidine plus ASA in reducing ischemic events in pts receiving coronary stents	through 12/00

Evidence Table A4. Systematic Reviews

Author Year	Aims	Time period covered
Hankey et al. 2000 (20)	establish how the thienopyridines (T and C) compare with ASA in terms of effectiveness and safety in the prevention of vascular events among pts at high risk of vascular disease	No date was reported although the paper was received March 10, 2000; final revision received April 21, 2000. The range of years that studies were included were 1983-2000 per reference section
Tran et al. 2004 (18)	Summarize the current state of evidence regarding antiplatelet treatment in pts with CV disease, CAD, and PAD, and to provide reasonable recommendations for clinical practice	1960-8/2004
Serebruany et al. 2004 (55)	determine the frequency of bleeding complications dependent on the class and dose of antiplatelet agent used observed in recently published mj RC trials	1988-2002

Evidence Table A4. Systematic Reviews

Author Year	Aims	Time period covered
Antithrombotic Trialists' Collaboration 2002 (44)	determine the effects of antiplatelet therapy among patients at high risk of occlusive vascular events	all trials, published or otherwise that were available by Sept 1997
Hankey et al. 2000 (20)	determine the effectiveness and safety of thienopyridine derivative (ticlopidine and clopidogrel) vs ASA for the prevention of serious vascular events (stroke, MI or vascular death) in pts at high-risk , specifically pts with previous TIA or ischemic stroke	all unconfounded, DB, R trials directly comparing ticlopidine or clopidogrel with ASA in high vascular risk pts. All trials were done within the last 20 years
Wilterdink and Easton 1999 (45)	Review and compare the results of ESPS-2 and previous studies of dipyridamole + ASA and aggregate them in a meta-analysis	1994 ATC trial + 1996 ESPS-2 trial
Bennett et al. 1999 (60)	review ticlopidine-associated hematologic toxic effects	clinical trials, MedWatch database from 1992 through 1997, published phase 3 clinical trials and case reports, hematologists, and plasmapheresis centers

Evidence Table A4. Systematic Reviews

Author Year	Aims	Time period covered
Hankey et al. 2001 (43)	review effectiveness and safety of the thienopyridines compared with aspirin for the prevention of vascular events among patients at high risk of vascular disease	"last 20 years"

Evidence Table A4. Systematic Reviews

Author Year	Eligibility Criteria
Casella et al. 2003 (34)	Medline (+ manual search of the references) search: , English-language 1. direct comparison of combination therapy with C and ASA vs. T + ASA combination after coronary stenting; 2. clear description of the study methods; 3. ability to extract data for different endpoints. The key words used were C, T and coronary stenting and their various combinations
Robless et al. 2001 (52)	Studies: DB, RCT by 1/99 of antiplatelet tx (ASA, dipyridamole, indubufen, sulphinpryaozone, picotamide, suloctidil, T and C) vs. placebo, or vs. other antiplatelet agents, in pts with stable intermittent claudication or critical ischemia (Fontaine stages II-IV) or undergoing vascular surgical intervention (surgery or PTA) were included. Search strategy included NLM Medline database from 1/66-1/99; Embase from 1/80-1/99 using the same terms, register of trials held by the APTC(1994), Cochran Controlled Trials Register in the Cochrane Library (including Medical Editors' Trial Amnesty Database, Proceedings from vascular surgical society mg, and pharmaceutical companies that market antiplatelet agents (T and C)
Bhatt et al. 2002 (33)	Medline search, English language that compared C +ASA vs. T + ASA. Medical subject headings and key words used were C, T and stents. Relevant abstracts and presentation from 1999 and 2000 AHA, ACC, European Soc. Of Cardiology and Transcather CV Therapeutics were identified. If results were published only in abstract form or presented orally or in a poster, data were verified with primary investigator.

Evidence Table A4. Systematic Reviews

Author Year	Eligibility Criteria
Hankey et al. 2000 (20)	all unconfounded randomized trials comparing either T or C with ASA for pts at high risk of vascular disease (symptoms of ischemia of the cerebral, coronary, or peripheral circulations) who were followed up for at least 1 month for the occurrence of vascular events
Tran et al. 2004 (18)	Studies 1. randomized; 2. recruited pts with established vascular disease (TIA, ischemic stroke, CAD and PAD), 3. compare an antiplatelet regimen with P or one antiplatelet regimen with another; and 4. assessed tx for at least 10 days. Key words related to antiplatelet agents (ASA, T, dipyridamole, C) and vascular disease (ACS, atherothrombosis, ischemic stroke, MI, PAD, TIA, unstable again) were used to search the MEDLINE database and trial registers of the Cochrane Groups. Journal and abstracts--manually searched and reference lists of trials and review articles were scrutinized. Meta-analysis and scientific statement of guidelines from official societies were also reviewed.
Serebruany et al. 2004 (55)	English; were retrieved from MEDLINE, OVID and CARDIOSOURCE. Only studies had f/u for at least 1 month and in which a full description of hemorrhagic complications were reported

Evidence Table A4. Systematic Reviews

Author Year	Eligibility Criteria
Antithrombotic Trialists' Collaboration 2002 (44)	randomized trials of an antiplatelet regimen vs control or of one antiplatelet regimen vs another in high risk patients.
Hankey et al. 2000 (20)	Al truly randomized trials in which a thienopyridine derivative (ticlopidine or clopidogrel) was compared directly with ASA, and in which pts were followed up prospectively and systematically for the occurrence of serious vascular events for at least one month were included.
Wilterdink and Easton 1999 (45)	2 trials (see previous entry)
Bennett et al. 1999 (60)	Not stated

Evidence Table A4. Systematic Reviews

Author Year	Eligibility Criteria
Hankey et al. 2001 (43)	All confounded randomized trials comparing either ticlopidine or clopidogrel with ASA among patients at high risk of vascular disease (those with symptoms of ischemia of the cerebral, coronary, or peripheral circulations) who were followed for at least one month for the recurrence of vascular events. Specialize trial registers of the Cochrane Stroke Group and the Antithrombotic Trialist's Collaboration, MEDLINE, and Embase were searched. Additional unpublished information and data was sought from Sanofi as well as the principal investigators of the CAPRIE trial.

Evidence Table A4. Systematic Reviews

Author Year	Number of Patients	Characteristics of Identified Articles: Study Designs
Casella et al. 2003 (34)	2736 in the randomized trials and 8952 pts in the registries trials. 11,688-efficacy analysis; 7165 for safety analysis	3 randomized trials and 7 registries were included. The 3 randomized trials were CLASSICS (the only double-blind study), TOPPS, and Mueller et al (1999)
Robless et al. 2001 (52)	6452 pts with IC, ABPI < 0.85, IC with previous leg amputation, bypass or angioplasty from the CAPRIE Trial would be the only one of interest	systematic review of 39 randomized controlled trials of antiplatelet therapy. 24 trials of antiplatelet tx v P in IC and 10 trials o antiplatelet tx vs. P in pts undergoing lower limb bypass surer. 2 trials antiplatelet tx vs. P in PVD pt undergoing PTA. 5 trials of ASA vs. a second antiplatelet tx in pts with PVD. 2 trials comparing antiplatelet tx vs. P as well as ASA vs. a second antiplatelet tx--as both of these trials had 3 study arms involving 2 antiplatelet tx and placebo. Only one study (CAPRIE-RCT. DB, AC, MC) meets the criteria for this drug class review
Bhatt et al. 2002 (33)	13955	meta-analysis; 3 randomized trials (CLASSICS), (TOPPS), and Muller 200-CIrculation 2000) and 7 single-center registries

Evidence Table A4. Systematic Reviews

Author Year	Number of Patients	Characteristics of Identified Articles: Study Designs
Hankey et al. 2000 (20)	22656 (9840-recent TIA or ischemic stroke; 6302 recent MI; 6514 symptomatic peripheral arterial disease)	specialized search trial registers (Cochrane Stroke Group and ATC, Medline, and Embase) and Sanofi was contacted. 4 trials- 3 trials with ASA vs. T (n=3471); and one trial with clopidogrel -CAPRIE (n=19185). CAPRIE and TASS (N Engl J Med 1989;321:501-7)- centralize, computer generated scheme with good preconcelment of tx allocation. Tohgi et al (Jpn J med 1987;26:117-119) and Schoop (Sanofi internal report)-said to be randomized but method not stated
Tran et al. 2004 (18)	30619-23000 (ACT) since it had primarily ASA = ~7619	111 trials, all were "randomized (see criteria)
Serebruany et al. 2004 (55)	~23232 (338,191 pts in meta-analysis)	72 trials were identified; 50 were eligible (see criteria). Most of the studies used TIMI criteria to assess bleeding severity. Criteria from GUSTO was also present--less common.

Evidence Table A4. Systematic Reviews

Author Year	Number of Patients	Characteristics of Identified Articles: Study Designs
Antithrombotic Trialists' Collaboration 2002 (44)	o (trial was mainly ASA, the combination of ASA and dipyridamole is not of the same formulation as the drug of interest	Not applicable
Hankey et al. 2000 (20)	4 trials involving a total of 22,656 high vascular risk pts. ASA vs ticlopidine in 3 trials (3471 pts) and clopidogrel in one trial (19,185)	4 trials involving a total of 22,656 high vascular risk pts. ASA vs ticlopidine in 3 trials (3471 pts) and clopidogrel in one trial (19,185)
Wilterdink and Easton 1999 (45)	6602	ATC-meta-anaylsis, ESPS-2 RCT
Bennett et al. 1999 (60)	98 cases of ticlopidine-associated TTP	2 large stroke preventions studies (Phase 3)-CATS, TASS; 2 large phase 3 clinical Stent trial

Evidence Table A4. Systematic Reviews

Author Year	Number of Patients	Characteristics of Identified Articles: Study Designs
Hankey et al. 2001 (43)	22656	4 randomized trials

Evidence Table A4. Systematic Reviews

Author Year	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Casella et al. 2003 (34)	All were stent pts. Of the randomized trials, all differed in their inclusion and exclusion criteria: CLASSICS study enrolled a very low risk population. The registries overall included a higher risk population.	6 trials of expophor 5 mg to 20 mg/day, 4 studies of zenophr 10mg to 30mg/day. The randomized and registries all differed in mode and length of therapy. The randomized trials intervention included 300mg C x1 (LD) or no loading dose+ 75mg/day x 3.73 wks; 300mg X1 (LD) + 75mg/day x 2 wks and 75mg C daily x 4 wks. 1 registry trial included in meta-analysis mode to therapy was not reported. 2 registries trials were 300mg C X1 + 75mg/day x 4 wks. 1 registry trial was 75mg/day for 2 or 4 wks; 1 registry trial was 300mg x 1 + 75mg/day x 2 wks; 1 registry trial was 150mg x 2 + 75mg/day x 4 wks; 1 registry trial was 300mg C X 1 or no loading dose + 75mg/day x 4 wks. Dose/duration of T and ASA were not indicated for any of the studies
Robless et al. 2001 (52)	Participants: All pts with stable PVD (Fontaine stage II) for more than 6 months or pts undergoing vascular surgical intervention (surgery or PTA) for PVD were included in the analysis. 6452 pts with IC, ABPI < 0.85, IC with previous leg amputation, bypass or angioplasty from the CAPRIE Trial would be the only one of interest	ASA 325mg vs. C 75mg x 12 months from CAPRIE
Bhatt et al. 2002 (33)	all were stent pts. Of the randomized trials, all differed in their inclusion and exclusion criteria:	All studies were C + ASA or T + ASA. Different among the registries and sometimes within the registries) as to whether pts were pretreated with thienopyridine before the procedure, whether LD were administered and whether the length of therapy was 14 or 28 days. CLASSICS--LD of C in one arm and therapy was administered within 6 h of completion of the procedure x 3.73 weeks; TOPPS used LD of both T and C, given after the procedure x 2 wks, Muller et al used a 500mg LD for T are only x 3.73 wks.

Evidence Table A4. Systematic Reviews

Author Year	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Hankey et al. 2000 (20)	CAPRIE-recent ischemic stroke, recent MI, or PAD; Tohgi-pts with recent TIA; Schoop-men with PAD and TASS-pts with recent TIA or minor ischemic stroke. Average age ~63 years, approximately 2/3 were male, and most were white	6 trials of expophor 5 mg to 20 mg/day, 4 studies of zenophr 10mg to 30mg/day. CAPRIE-C 75mg daily vs. ASA 325mg daily x 23 months; Tohgi-T 200mg daily vs. ASA 1500mg daily X 12 months; Schoop T 500mg daily vs. ASA 1500mg daily X 24 months and TASS T 500mg daily vs. ASA 1300mg daily x 40 months
Tran et al. 2004 (18)	22 trials with TIA or stroke (n=30619), 47 trials with CAD pts (n=59821) and 42 trials with PAD (n=9214). One table indicated n= 19302 for MI, previous MI n=20006; unstable angina n=5031; stable angina/CAD n=2920	21 trials ASA ,T, dipyridamole, ASA + dipyridamole in TIA/stroke trials; 46 trials included ASA, T, dipyridamole, ASA + dipyridamole in CAD; 42 trials ASA, T, dipyridamole, ASA + Dipyridamole, picotamide in PAD. No specific data was provided for dose; duration etc. All the trials were vs. P or one antiplatelet regimen with another
Serebruany et al. 2004 (55)	(In all 50 trials) Most had AVS (unstable angina and acute MI). A few trials involved HTN pt, and about 40% were PTCA. About 85% of pts were enrolled in US.	ASA < 100mg (6 listed on table which includes ESPS2; 3 trials mentioned in text; ASA ≥ 100mg (9 trials) ; dipyridamole (including Aggrenox) ESPS -2 listed twice on table; # trials not mentioned in text, ADP receptor blockers (10 trials) ; IV GP 2b/3A (18 trials) and oral GP 2b/3a inhibitors(7 trials)

Evidence Table A4. Systematic Reviews

Author Year	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Antithrombotic Trialists' Collaboration 2002 (44)	Not applicable	6 trials of expophor 5 mg to 20 mg/day, 4 studies of zenophr 10mg to 30mg/day. Not applicable
Hankey et al. 2000 (20)	Patients were on average about 63 years of age, and about 2/3 were men.43% -TIA or ischemic stroke, 28% MI, 29% PAD	1 trial-(CAPRIE)-19,185 pts with ischemic stroke 6431, recent MI 6302, PAD 6452) and3 trials with ticlopidine
Wilterdink and Easton 1999 (45)	6602 pts with cerebral ischemia dn recorded 824 strokes.	1 trial and 1 meta-analysis that contained 14 trials that compared the combination of dipyridamole and ASA (different agent than what was used in ESPS-2 vs ASA
Bennett et al. 1999 (60)	56 cases in stroke prevention-mean age 66.9±11.8).42 cases in stent setting--mean age 62.4±11.5	stent/cva populations. Ticlopidine has been used less than 2 weeks in 5.4% and 2.4%, between 2 and 3 weeks in 17.9% and 21.4%, between 3 and 4 weeks in 30.4% and 38.1% and between 4 and 12 weeks in 46.4% and 38.1%.

Evidence Table A4. Systematic Reviews

Author Year	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Hankey et al. 2001 (43)	ASA vs ticlopidine in 3 trials (n=3,471) and with clopidogrel in 1 trial (n=19,185 pts). Recent TIA or ischemic stroke was the qualifying event in 9840 pts, a recent MI in 6,302 pts, and symptomatic PAD in 6,514 pts. Average age was approx. 63, with approx. 2/3 of the pts being male and white.	6 trials of extended-release dipyridamole 200mg/day, 4 studies of extended-release dipyridamole 400mg/day, 6 trials of expophor 5 mg to 20 mg/day, 4 studies of zenophil 10mg to 30mg/day. ASA vs ticlopidine in 3 trials (n=3,471) and with clopidogrel in 1 trial (n=19,185 pts).

Evidence Table A4. Systematic Reviews

Author Year	Main Results
Casella et al. 2003 (34)	Study Endpoints: Efficacy Evaluation and Safety Evaluation: Efficacy: composite of death and non-fatal MI. (pre-specified outset of the analysis). The secondary endpoint was a composite of MACE (mg adverse cardiac events, according to the definition used in the single studies. The def. differed although it was mostly a combination of death, non-fatal MI, TVR (target vessel revascularization or subacute stent thrombosis). Rates were pooled and analyzed as individual endpoints. At 30 days, C was associated with a significant decrease in the occurrence of death or non-fatal MI from 3.4 to 1.6% (OR 0.63, 95% CI 0.47 to 0.85, p=0.003). There was a trend (OR 0.83, 95% CI 0.66 to 1.03, p=0.1) toward less MACE in pts receiving C (2.7%) instead of T (3.8%), less mortality (OR 0.70, 95% CI 0.40 to 1.25, p = 0.2), and less non-fatal MI (OR 0.76, 95% CI 0.54 to 1.07, p = 0.1).
Robless et al. 2001 (52)	5 trials comparing one antiplatelet regimen against ASA in pts with PVD. 292 (8.4%) of 3467 pts in the ASA group suffered a vascular event. In the seconds antiplatelet regimen (T500mg, C 75mgor dipyridamole/ASA [in doses of 330mg/75mg; 600mg/225mg;990mg/225 respectively] 227 (6.6%) of 3461 pts suffered a vascular event.
Bhatt et al. 2002 (33)	30 day major adverse cardiac events (MACE), as defined in each trial, was the prespecified primary endpoint. MACE+ death, MI, TVR or subacute stent thromosis (SAST) in all studies except CLASSICS and 2 registires. Secondary end point was all-cause mortality. Pooled data: OR 0.51 (95% CI 0.42 to 0.63). 50% RR in the MACE in C + ASA vs T + ASA (2.10% vs. 4.04%) was SS p=0.001). The reduction in the MACE was seen in randnomized and registry data but was only substantial and SS in the registries. The OR in favor of C in the randomized trials was 0.90 (95% CI 0.57 to 1.44) The OR in favor of C in the larger numbers of pt in the registires was 0.45 (95% CI 0.36 to 0.57, p=0.001). MORTALITY: OR in favor of C was 0.44 (95% CI 0.29 to 0.67)--56% reduction in mortality in those pt treated with C and ASA vs T and AA 90.48 vs 1.09%, p=0.001). If look at just the randomized trials, the OR in favor of C was 0.47 (95% CI 0.17 to 1.30, p=0.14). The registy data produced an OR of 0.45 in favor of C (95% CI 0.28 to 0.70, p=0.001). Meta-anlysis (adjust for heterogeneity) for both MACE C 0.72 (0.59 to 0.89, p=0.002) compared with T. OR for rate of mortality was 0.55 in favor of C (0.37 to 0.82, p=0.003)

Evidence Table A4. Systematic Reviews

Author Year	Main Results
Hankey et al. 2000 (20)	OR of a serious vascular disease (stroke, MI or vascular death) 12.0% for theinopyridine vs. 13% for ASA; OR 0.91, 95% CI 0.84 to 0.98; 2p=0.01 which corresponds to the prevention or delay of 11 (95% CI 2 to 19) vascular events per 1000 pt treated for 2 years. Reduction in the odds of any stroke (5.7% vs. 6.4% for ASA; or 0.88, 95% CI 0.79 to 0.98, corresponding to the prevention or delay of 7 (95% CI 1 to 13) strokes per 1000 pts treated for 2 years. There was a NS trend toward a reduction in ischemic stroke (OR, 0.90, 95% CI 0.81 to 1.01), MI infarction (OR 0.88, 95% CI 0.76 to 1.01), vascular or unknown cause of death (OR 0.93, 95% CI 0.82 to 1.06), and death from any cause (OR 0.95, 95% CI 0.85 to 1.05)
Tran et al. 2004 (18)	TIA or STROKE; ASA-ATC (meta-analysis) provided most of the data-23,000 pts with antiplatelet therapy (usually ASA) compared with P or untreated control OR 22 (15.2 to 27.5) p<.001 in ischemic stroke, MI or vascular death. ATC was for mean 29 months--was associated with 22% reduction in recurrent ischemic stroke, MI or vascular death (17.6% vs. 21.4%, p <.001) TICLOPIDINE and CLOPIDOGREL: T Studies: CATS-1072 pts, T 500mg/day compared with P or untreated control reduced the risk of stroke, MI or vascular death by 23% (11.3% vs. 14.0%, p=.02) after 2 years of f/u.TASS-3069 pts with TIA or minor stroke (1300mg/day) reduced the risk of nonfatal stroke or death by 12% (17% vs. 19%), p=.02 after 3 years of follow-up. Diarrhea and rash (25%) and serious hematologic adverse effects, including neutropenia (1-2%) and TTP (0.025%-0.05%) have been reported in other studies (Hankey, Bennett, Hass). C study: CAPRIE: For all pts: reduction of stroke, MI or vascular death by 8,7% (95% CI 0.3 to 6.5; p=.04) For specifically ischemic stroke, RRR was similar and NS different from overall results. MATCH: ASA 75mg + C 75mg vs. C in 7599 pt with recent TIA or ischemic stroke. Combination of ASA and C did not significa
Serebruany et al. 2004 (55)	low-dose ASA and dipyridamole was associated with lowest risk (3.6 and 6.7% respectively) . TOTAL Rates of Bleeding (includes mj, minor, stroke, GI) Dipyridamole: 2 trials, N= 3,304 6.7% rate; 95% CI 5.8%, 8.5%); Plavix (7 trials) n= 19,191; 8.5% rate and 95% CI 8.1, 8.8%

Evidence Table A4. Systematic Reviews

Author Year	Main Results
Antithrombotic Trialists' Collaboration 2002 (44)	Not applicable
Hankey et al. 2000 (20)	High vascular risk pts: composite outcome stroke, MI OR vascular death, 12% vs. 13% [OR0.91, 95% CI:0.84 to 0.98)-NNT 11/1000 (95% CI 2-19), Fatal and non-fatal stroke 5.7% vs 6.4%, (OR 0.88, 95% CI:0.79 to 0.98)-NNT7(95% CI 1-13 strokes per 1000.
Wilterdink and Easton 1999 (45)	ESPS-2 + 14 trials of dipyridamole + ASA vs ASA alone, the combination reduces the risk of stroke by 23% over ASA alone.
Bennett et al. 1999 (60)	Death in 60% not receiving plasmapheresis compared with 21.9% of patients receiving plasmapheresis for stroke prevention and 14.3% of patients receiving plasmapheresis in the stent setting.

Evidence Table A4. Systematic Reviews

Author Year	Main Results
Hankey et al. 2001 (43)	pts at high risk of vascular disease: odds of a serious vascular events with thienopyridine compared with ASA, 12 vs 13, OR 0.91, 95% CI 0.84-.98, p=.01--NNT 11/1000 tx for 2 years (95% CI 2-19). Odds of suffering any stroke were reduced in favor of thienopyridine group (5.7% vs. 6.4%; OR 0.88, 95% CI 0.79-0.98) compared with ASA,,NNT 7 strokes/1000 patients. Reduction in ischemic stroke (OR 0.90, (0.81-1.01), MINOR 0.88, (0.76-1.01), vascular or unknown cause of death (OR 0.93, 0.82-1.06) and death from any cause (OR, 0.85-1.05)

Evidence Table A4. Systematic Reviews

Author Year	Subgroups
Casella et al. 2003 (34)	When the analysis was limited to 3 randomized trials, the % of pts who reached the primary endpoint in the C group (19/1529; 1.2%) was similar to that of the T group (15/1207; 1.2%) (OR 1.05, 95% CI 0.52 to 2.12, p= 0.9). However there was a trend toward a lower death rate for pts treated with C (6/1529, 0.4%) than those treated with T (9/1207; 0.7%) (OR 0.60, 95% CI 0.21 to 1.70, p=0.3). This datum was consistent with the death rate reported in the registries.C *Loading dose (7 studies) vs. no loading C dose (4 studies)* : a significant advantage for all endpoints was seen. (ODDS RATIO PLOTS ON PG 681--blurred-unable to read it. CLASSICS trial--when each arm was analyzed, no difference in the rate of death or non-fatal MI of C compared to T (1.1 vs 0.6% for the no loading dose, p=0.7, and 0.9 vs 0.6% , p =0.9 for the LD C arm vs. T. The group that had AMI tended to be slighlty older, more men, high rate of prior cardiac surgery and CHF (data not shown)More DM, histoty of angia pectoris, AMI or ischemic stroke also had a higher prevalence in the group with AMI and a BL CR in the upper quartile > 1.3 mg/dL)
Robless et al. 2001 (52)	CAPRIE--215 (6.7%) of 3223 pts in C suffered a vascular event compared with 277 (8.6%) of 3229 pts in the ASA group. In this CAPRIE subgroup the odds ratio for vascular events was 0.77 (95% CI 0.64-0.92) favoring clopidogrel p= 0.0028)
Bhatt et al. 2002 (33)	None reported

Evidence Table A4. Systematic Reviews

Author Year	Subgroups
Hankey et al. 2000 (20)	Among the 9840 TIA/ischemic stroke, vascular events (16.8% for theinopyridine vs. 18.3% for ASA; OR 0.90, 95% CI 0.81 to 1.00); stroke (10.4% thienopyridine vs. 12.0% for ASA; OR 0.86, 95% CI 0.75 to 0.97). Absolute reduction of 14 (95% CI -1 to 29) vascular events/1000 pts treated for ~2 years was similar to that observed among all high-risk pts. risk of stroke among pts with a previous TIA or ischemic stroke in the ASA group (12.0%) was almost twice as high as that for all high-risk pts (6.4%) Absolute reduction of 16 strokes (95% CI 3 to 28) per 1000 pts was approximately twice as large as that for all high-risk pts combined.
Tran et al. 2004 (18)	open-label: n=652 pt with unstable angina: T compared with control reduced the risk of death or Mi by 46% at 6 months p = .009 Balsano: Circulation 1990;336:827-830. There is a section in article specifically addressing STEMI--go back and review if needed
Serebruany et al. 2004 (55)	

Evidence Table A4. Systematic Reviews

Author Year	Subgroups
Antithrombotic Trialists' Collaboration 2002 (44)	Not applicable
Hankey et al. 2000 (20)	TIA or ischemic stroke pt: several vascular events (from 3 trials)16.8 vs 18.3% with ASA; (OR:0.90, 95% CI 0.81 to 1.00, corresponding to the avoidance of 14 per 1000 pts treated for 2 years
Wilterdink and Easton 1999 (45)	Non-fatal stroke (ESPS-2 trial + 9/14 meta-analysis trials:)-p=.005 in favor of dipyridamole + ASA.
Bennett et al. 1999 (60)	ticlopidine-associated TTP in the stroke prevention setting were more likely to be women 62.5% vs 28.6%, p=.01

Evidence Table A4. Systematic Reviews

Author Year	Subgroups
Hankey et al. 2001 (43)	pts restricted presenting with stroke or TIA--thienopyridine and ASA produced similar benefits for the composite of all vascular events (16.8% vs 18.3% for ASA, or0.90, 95% CI0.81-1.00) corresponding to the NNH 14 serious vascular events per 1000 pts treated x 2 years. The risk of any stroke was decreased in the thienopyridine group compared with ASA (10.4% vs 12.%, OR 0.86, 95% CI 0.75-0.97) corresponding to 16 (95% CI3-28) strokes avoided per 1000 pts treated.

Evidence Table A4. Systematic Reviews

Author Year	Adverse Events	Comments
Casella et al. 2003 (34)	Safety analysis: At 30 days there was a 47% reduction in the occurrence of major adverse SE (OR 0.53, 95% CI 0.42 to 0.66, p < 0.00001) in pts treated with C + ASA. Incidence of drug intolerance was significantly reduced a month pts on C + ASA (OR 0.51, 95% CI 0.36 to 0.72, p < 0.0001). Fewer C pts developed neutropenia or thrombocytopenia (OR 0.58, 95% CI 0.71 to 1.99, p = 0.5)	CLASSICS study was a safety study involving 3 arms comparing a LD vs. no LD of clopidogrel vs. T. The published trial pooled both C arms, but for this analysis, each arm was considered independently. Randomized vs. registry studies and LD vs. no LD data were analyzed. TOPSS study did not report the rate of non-fatal MI, leaving only 2 randomized trials suitable for the combined endpont analysis. Unable to read Figure 1 and 2 (Odds ratio plots)---blurred. I
Robless et al. 2001 (52)	In the 5 trials of ASA compared to other antiplatelet agents (see I for description)68 (2%) of 3467 pts in the ASA group had mj bleed vs. 50 (1.4%) of 3561 pt. NS	Study was supported by BJS Research Bursary 1997
Bhatt et al. 2002 (33)	None reported	Nice OR plots comparing each study for the rate of 30 day MACE as well as for the pooled data AND for the 30 day mortality

Evidence Table A4. Systematic Reviews

Author Year	Adverse Events	Comments
Hankey et al. 2000 (20)	no clear difference btw the theinopyridines and ASA in the odds of experiencing an intracranial hemorrhage (0.3% vs. 0.4% ASA); (OR 0.82, 95% CI 0.53 to 1.27) or an extracranial hemorrhage (8.8% vs 8.9% ASA; OR 1.00, 95% CI 0.91 to 1.09). C and T were associated with a significant reduction in the odds of GI hemorrhage (1.8% vs 2.5%; OR 0.71, 95% CI 0.59 to 0.86) and of indigestion/N/V (14.8% for T or C vs 17.1% for ASA, OR 0.84, 95% CI 0.78 to 0.90) but with and increased odds of diarrhea and or skin rash. Compared to ASA, T produced an 2 fold increase in the odds of skin rash 11.8% for T vs 5.5% for ASA; OR 2.2 95% CI 1.7-2.9) and diarrhea (20.4% for T vs 9.9% for ASA; OR 2.3, 95% CI 1.9 to 2.8) whereas C produced a smaller increase of approx 1/3 in the odds of skin rash (6.0% for C vs 4.6% for ASA; OR 1.3, 95% CI 1.2 to 1.5) and of diarrhea (4.5% for C vs 3.4% for ASA, OR 1.3, 95% CI 1.2.to 1.6). Neutropenia (<1.2x 109/L 2.3% T vs. 0.8% ASA; OR 2.7, 95% CI 1.5 to 4.8) C 0.1% vs 0.2 ASA; OR 0.63, 95% CI 0.29 to 1.36; Thrombocytopenia < 100x 109 pts/L 0.26% vs 0.26%; OR 1.00; 95% CI 0.57 to 1.74) No published tria available for the frequnecy of thrombocytopenia associated with T compared with ASA	Most of the data were from the 2 largest trials-CAPRIE, TASS. Conclusion per article 1. theinopyridine provide sl. More protection than does ASA against vasc events among high-risk pts, but the extent of added benefit is uncertain, both overall and especially for individual pts. 2. C appears to be safer than T. 3. C is at least as safe as ASA.
Tran et al. 2004 (18)	NSTEMI ACE: CURE trial: C + ASA -mj bleeding (3.7% vs. 2.7%; RRR, 1.38;95% CI 1.13 to 1.67; p=.001) but no significant excess in life-threatening bleeding (2.1% vs. 1.8%; p=.13) Incidence of bleeding with C was lower in pts receiving ASA ,100mg.d vs. higher dose	ER form of dipyridamole was used in ESPS-2 vs. short-acting dipyridamole in other studies. ESPIRT (European/Australian Stroke Prevention in Reversible Ischemia Trial, n=4500, ER-DP 400mg/d + ASA (30-325mg/d) vs. ASA alone in pt s/p TIA or minor ischemic stroke a and ProFESS trial-Prevention Regimen for Effectively Avoiding Second Strokes n=15500l C + ASA vs. ER-DP + ASA in pt with ischemic TIA or stroke--no effervescences were provided. No studies have compared C with P/control (in the absence of ASA) in pt with NSTEMI ACS.References for PTCA: PCI-CURE Lancet 2001358:527-533 and CREDO-JAMA 2002:288:2411-2420. There is a section in this article about STEMI that was not extracted---GO BACK IF NEEDED
Serebruany et al. 2004 (55)	Major Bleeding: Dipyridamole 2 trials:, 3,304 pts, 1.0% rate (f) (95% CI 0.7%, 1.3%). Thienopyridines- 8 trials; 18,574 pts; rate 2.1%; (1.9%, 2.3%). MINOR Thienopyridine (1 trial, n= 6259) 5.1% rate (4.6, 5.7) Stroke (bleeding) Thienopyridine 2 trials, 15,858 pts; 0.3% rate and 95% CI 0.2%,0.3) GI bleeding: Thienopyridine 5 trials, N= 17,824; 1.6% rate; 95% CI, 1.4%, 1.8%).	

Evidence Table A4. Systematic Reviews

Author Year	Adverse Events	Comments
Antithrombotic Trialists' Collaboration 2002 (44)	Not applicable	
Hankey et al. 2000 (20)	Neutropenia-2 trials--ticlopidine 2.3% vs 0.8% with ASA(2.7, 95% CI 1.5 to 4.8)Rash: clopidogrel6.0% vs 4.6% (OR 1.3, 95% CI: 1.2 to 1.5) and ticlopidine 11.8% vs 5.5% [OR 2.2, 95% CI 1.7 to 2.9)	
Wilterdink and Easton 1999 (45)	Not stated	ATC trial did not have the same formulation as the agent used in ESPS-2 trial
Bennett et al. 1999 (60)	Normal platelet counts within 2 weeks of the onset of Top were documented in most patients in both groups. Ticlopidine had been used < 2 weeks in 5.4% and 2.4% in stroke prevention and stent placement respectively; between 3-4 weeks in 30.4 and 38.1% and between 4-12 weeks in 46.4 and 38.1 respectively.	

Evidence Table A4. Systematic Reviews

Author Year	Adverse Events	Comments
Hankey et al. 2001 (43)	intracranial hemorrhage (0.3 vs. 0.4%l OR 95% CI 0.53-1.27) Extracranial hemorrhage (8.8% vs 8.9% for ASA; OR 1.00, 95% CI 0.91-1.09. gastrointestinal hemorrhage 1.8% vs 2.5% for ASA; OR 0.71, 95% CI 0.59-0.86) and indigestion/n/v 14.8% vs. 17.1%, OR 0.84, 95% CI 0.78-0.90. The odds of diarrhea or skin rash were increased in the thienopyridine A vs. C skin rash 6.0% vs. 4.6%; OR 1.3, 95% CI 1.2-1.5) and diarrhea (4.5% vs. 3.4%, OR 1.3, 95% CI 1.2-1.6). A vs. T: skin rash (11.8% vs. 5.5%, OR 2.2,95%CI 1.7-2.9) diarrhea (20.4% vs. 9.9%, r 2.3, 95CI 1.9-2.8). Neutropenia with ticlopidine was 2.3% vs. 0.8% with ASA; OR ,95% CI 1.5-4.8. No increased risk was observed with C compared with ASA (0.1% vs. 0.2%; OR 0.63, 95% CI 0.29-1.36)	