

Drug Class Review

Newer Antiplatelet Agents

Final Update 2 Report
Executive Summary

June 2011



The purpose of the Executive Summary is to summarize key information contained in the Drug Effectiveness Review Project report “Drug class review: Newer antiplatelet agents”, dated June 2011. The full report can be accessed at the following web address: <http://derp.ohsu.edu/about/final-document-display.cfm>. Readers are advised to review the full report. The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. They are not intended to provide any legal or business advice. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Update 1: January 2007
Original Report: November 2005

Update 2 Authors:

Kathy Ketchum, BPharm, MPA:HA

Kim Peterson, MS

Sujata Thakurta, MPA:HA

Allison Low, BA

Marian S. McDonagh, PharmD

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Copyright © 2011 by Oregon Health & Science University
Portland, Oregon 97239. All rights reserved.



INTRODUCTION

Atherosclerosis often starts in late adolescence or early adulthood, although clinical manifestations typically occur years later. Statistics from 2008 indicate that approximately 82.6 million Americans have at least 1 type of cardiovascular disease including ischemic coronary heart disease, stroke, and/or peripheral arterial disease. Although there are various approaches to secondary prevention of vascular disease, a principal component is the use of antiplatelet agents. While aspirin has been considered a standard agent for many years in some populations, over the past decade or more, newer antiplatelet agents have come to the forefront as adjuncts to or substitutes for aspirin in many clinical situations.

Scope and Key Questions

The goal of this report is to compare the effectiveness and harms of newer antiplatelet agents for treatment of adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease, and to determine if there are any subgroups of patients based on demographics, socioeconomic status, other medications, or comorbidities for which any included drugs are more effective or associated with fewer harms. Included drugs are shown in Table 1.

Table 1. Included interventions

Drug	Trade name	Dosing
Aspirin 25 mg/ extended-release dipyridamole 200 mg	Aggrenox [®]	One capsule bid in patients at risk for stroke after transient ischemia of the brain or completed ischemic stroke due to thrombosis
Clopidogrel ^a	Plavix [®]	<p>Acute Coronary Syndrome <u>Non-ST Elevation MI</u>: 300 mg loading dose, continue at 75 mg qd in combination with ASA 75 to 325 mg qd <u>ST Elevation MI</u>: 75 mg qd in combination with 75-325 mg ASA with or without thrombolytics; Plavix[®] may be initiated with or without a loading dose</p> <p>Recent MI, recent stroke or established PAD 75 mg qd</p> <p>CYP2C19 Poor Metabolizers or Use with a Proton Pump Inhibitor Appropriate dose regimen has not been established</p>
Prasugrel	Effient [™]	60 mg loading dose then 10 mg qd in combination with ASA 75-325 mg; patients <60 kg should lower maintenance dose to 5 mg
Ticlopidine ^a	Generic only	<p>Stroke 250 mg bid</p> <p>Coronary artery stenting 250 mg bid with ASA for 30 days of therapy following stent implantation</p>

^a As monotherapy or in combination with aspirin (ASA).

Abbreviations: ACS, acute coronary syndrome; ASA, Aspirin; bid, twice daily; MI, myocardial infarction; NSTEMI, non-ST Segment Elevation Myocardial Infarction, PAD, peripheral arterial disease; PPI, proton pump inhibitor; qd, once daily; STEMI, ST Segment Elevation Myocardial Infarction.

The participating organizations of the Drug Effectiveness Review Project approved the following key questions to guide the review for this report:

1. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in effectiveness?
2. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in harms?
3. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in effectiveness and harms based on duration of therapy?
4. Are there subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one antiplatelet agent is more effective or associated with fewer harms?

METHODS

To identify articles relevant to each key question, we searched Medline (1994 to December 2010), Embase (1994 to May 2006), the Cochrane Database of Systematic Reviews[®] (2005 to December 2010), the Cochrane Central Register of Controlled Trials[®] (4th Quarter 2010), and Database of Abstracts of Reviews of Effects[®] (4th Quarter 2010), and reference lists of included studies. In electronic searches, we combined terms for drug names, indications, and included study designs, all limited to human and English language. In addition, we searched the US Food and Drug Administration Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review.

We assessed the internal validity (quality) of all studies using predefined criteria based on study design (see www.ohsu.edu/drugeffectiveness). We also determined the quality of studies to be *good, fair, or poor* based on predefined criteria. We graded the overall strength of a body of evidence pertaining to a particular key question or outcome based on the approach proposed in the Evidence-based Practice Center Methods Guide. This approach considers the risk of bias of the studies, consistency of results, directness of evidence, and precision of pooled estimates resulting from the set of studies relevant to the question. Strength of evidence was graded as High, Moderate, Low, and Insufficient.

RESULTS

Overview

For Update 2, literature searches identified 1705 citations. We received dossiers from 1 pharmaceutical manufacturer, Eli Lilly and Company. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 245 citations. After reapplying the criteria for inclusion, we ultimately included 39 publications, representing 29 unique studies.

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

We found no head-to-head trials of newer antiplatelet agents for acute coronary syndrome managed medically only or peripheral vascular disease.

In patients with acute coronary syndrome managed with coronary revascularization via stenting or bypass grafting, the TRITON-TIMI 38 trial provided moderate- to high-strength evidence that prasugrel is similar to clopidogrel for reduction of all-cause mortality and cardiovascular mortality at 15 months. It also provided high-strength evidence that prasugrel reduces the risk of target-vessel revascularization at 15 months. There was low-strength evidence of no significant difference between ticlopidine and clopidogrel in revascularization for periods up to 6 months. There was also low-strength evidence that the difference between ticlopidine and clopidogrel in cardiovascular mortality was not significant at 30 days.

In patients with acute coronary syndrome who are managed medically, there was moderate-strength indirect evidence from CURE that there is no significant difference between clopidogrel plus aspirin compared with aspirin alone in reduction of all-cause mortality at 12 months, but there was a significantly greater reduction in myocardial infarction with clopidogrel plus aspirin. In addition, CURE and CHARISMA both found no significant advantage for clopidogrel plus aspirin over aspirin alone in reducing risk of cardiovascular mortality at 12 months (moderate strength) and 28 months (low strength) and CAPRIE found no significant advantage for clopidogrel alone over aspirin alone in reducing risk of cardiovascular mortality at 22.8 months (low strength).

For treatment following stroke or transient ischemic attacks, the PRoFESS trial provided high-strength evidence that extended-release dipyridamole plus aspirin failed to demonstrate noninferiority compared with clopidogrel for the primary outcome of recurrent stroke and that there was no significant difference between extended-release dipyridamole plus aspirin and clopidogrel on the secondary outcomes of all-cause mortality and cardiovascular mortality. There was also moderate-strength evidence of no significant difference between clopidogrel and ticlopidine in reduction of all-cause mortality, cardiovascular mortality, or cerebral infarction over 52 weeks. Indirect evidence from aspirin-controlled trials of newer antiplatelet agents was consistent with direct evidence from head-to-head trials in suggesting no significant differences in effectiveness between extended-release dipyridamole plus aspirin and clopidogrel or between clopidogrel and ticlopidine for stroke or transient ischemic attack. Low-strength evidence suggested that clopidogrel plus aspirin, taken immediately following transient ischemic attack or

minor stroke, does not significantly reduce the risk of stroke compared with aspirin alone. Larger studies are needed to confirm or refute these findings.

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

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

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

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

In patients with acute coronary syndrome managed medically, there was moderate-strength, indirect evidence of increased risk of major bleeding at 12 months with clopidogrel plus aspirin compared with aspirin alone from CURE.

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

Low-strength evidence from aspirin-controlled trials suggested that clopidogrel plus aspirin, taken immediately following transient ischemic attack or minor stroke, does not significantly reduce the risk of severe extracranial bleeding with clopidogrel compared with taking aspirin alone. But, major bleeding and withdrawals due to adverse events were not reported.

For patients with peripheral vascular disease, compared with aspirin alone, major bleeding risk was not significantly increased during dual therapy with clopidogrel plus aspirin. Incidence of withdrawals due to adverse events was not reported.

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

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

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

There was no significant interaction between age or sex and the relative effects of prasugrel and clopidogrel on the primary composite endpoint (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) but a post-hoc analysis suggested no net benefit from prasugrel for patients 75 years of age or older.

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

A subgroup analysis of the TRITON-TIMI 38 trial found that, compared with clopidogrel, there was a significantly greater reduction in risk of the composite primary endpoint with prasugrel in patients with and without diabetes. In a post-hoc analysis of TRITON-TIMI 38, it was suggested that patients who had a previous stroke or transient ischemic attack had net harm from prasugrel and patients weighing less than 60 kg had no net benefit from prasugrel.

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

The increased risk of nonfatal and fatal bleeding with clopidogrel plus a Vitamin K antagonist was almost 3 times higher than with Vitamin K antagonist alone, and was similar to the risk with triple therapy (aspirin, clopidogrel, Vitamin K antagonist).

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

SUMMARY

The main findings of this review are summarized in Table 2. One potential limitation to the applicability of the findings of this review is that they relate to a narrower range of drugs than are available in clinical practice. The selection of drugs included in this review was influenced by the specific programmatic interests of the organizations participating in the Drug Effectiveness Review Project and are not meant to be read as a usage guideline. Of the drugs studied, trials differed with respect to dosing regimens limiting any conclusions about optimal dose.

Table 2. Summary of the evidence by key question

Key Question	Strength of evidence	Conclusion
Key Question 1. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in effectiveness?		
ACS medically managed	Clopidogrel/aspirin vs. placebo/aspirin: Moderate	No difference between placebo/aspirin and clopidogrel/aspirin at reducing all-cause mortality and cardiovascular mortality at 12 months
	Clopidogrel/aspirin vs. placebo/aspirin: Moderate	Significant difference in reduction of MI at 12 months
	Clopidogrel/aspirin vs. placebo/aspirin: Low	No significant difference in reduction of cardiovascular mortality at median 28 months
	Clopidogrel vs aspirin: Low	No significant difference in reduction of cardiovascular mortality at mean 1.9 years
ACS coronary interventions	Prasugrel/aspirin vs. clopidogrel/aspirin: High	Prasugrel reduced risk of target-vessel revascularization at 15 months when compared with clopidogrel
	Prasugrel/aspirin vs. clopidogrel/aspirin: Mod-High	No difference in risk of all-cause mortality and cardiovascular mortality at 15 months
	Ticlopidine/aspirin vs. clopidogrel/aspirin: Low-Moderate	No difference in risk of target-vessel revascularization at 30 days and 6 months
	Ticlopidine/aspirin vs. clopidogrel/aspirin: Low	No difference in risk for cardiovascular mortality at 30 days
Stroke/transient ischemic attack	Extended-release dipyridamole/aspirin vs. clopidogrel: High	No significant difference for all-cause mortality, cardiovascular mortality, and recurrent stroke

Key Question	Strength of evidence	Conclusion
Peripheral vascular disease	Clopidogrel vs. ticlopidine: Moderate	No significant difference for all-cause mortality, cardiovascular mortality or cerebral infarction
	Clopidogrel vs. aspirin: Moderate	No significant difference for cardiovascular mortality
	Clopidogrel plus aspirin vs. aspirin alone: Low	No significant difference for all-cause mortality, cardiovascular mortality, and revascularization.
Key Question 2. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in harms?		
ACS medically managed	Clopidogrel/aspirin vs. placebo/aspirin: Moderate	Increased risk of major bleeding at 12 months
ACS coronary interventions	Prasugrel/aspirin vs. Clopidogrel/aspirin: Moderate	Increased risk of major bleeding with prasugrel and no difference in withdrawal due to adverse events at 15 months
	Ticlopidine/aspirin vs. clopidogrel/aspirin: Moderate	No difference in risk of major bleeding at 28 days
	Ticlopidine/aspirin vs. clopidogrel/aspirin: Low	Increased withdrawals due to adverse events with ticlopidine and no difference in risk of major bleeding at 6 months
Stroke/transient ischemic attack	Extended-release dipyridamole/aspirin vs. clopidogrel: Moderate to high	Lower rate of major bleeding and withdrawal due to adverse events with clopidogrel
	Clopidogrel vs. ticlopidine: Moderate	Lower rate of neutropenia and withdrawals due to adverse events with clopidogrel and no significant difference in rate of major bleeding
Peripheral vascular disease	Clopidogrel vs. aspirin: Insufficient	No data for peripheral arterial disease subgroup
	Clopidogrel plus aspirin vs. aspirin alone: Low	No significant difference for major bleeding
Key Question 3. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease do antiplatelet agents differ in effectiveness and harms based on duration of therapy?		
ACS coronary interventions	Clopidogrel 1 month vs. clopidogrel 6 months: Moderate	Significantly lower risk of revascularization with 6 months of therapy, no significant increase in bleeding risk, and nonsignificant benefit for all-cause mortality and cardiovascular mortality
	Clopidogrel 1 month vs. clopidogrel/average 8 months: Moderate	Smaller, nonsignificant benefit for revascularization with 8 months of therapy compared with 1 month and a trend toward increase in bleeding risk
	Clopidogrel 1 month vs. clopidogrel 12 months: Low	Further reduction in benefit for revascularization with 12 months of therapy and further, but nonsignificant increase in risk of bleeding
Key Question 4. Are there subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one antiplatelet is more effective or associated with fewer harms?		
Demographics	Clopidogrel vs. prasugrel: Low	There was no significant interaction between age or sex and the relative effects of prasugrel and clopidogrel on the primary composite endpoint (death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke)
	fixed-dose combination of extended-release dipyridamole plus aspirin vs. clopidogrel: Low	The fixed-dose combination of extended-release dipyridamole plus aspirin did not meet predefined criteria for noninferiority compared with clopidogrel for the primary outcome of recurrent stroke across all patients in the PROFESS trial, and the relative difference between antiplatelet drugs was consistent across subgroups based on age, race, and sex

Key Question	Strength of evidence	Conclusion
Comorbidities	Clopidogrel vs. prasugrel: Low	There was no significant interaction between presence of diabetes and the relative effects of prasugrel and clopidogrel on the primary composite endpoint (death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke)
	Fixed-dose combination of extended-release dipyridamole plus aspirin vs. clopidogrel: Low	The fixed-dose combination of extended-release dipyridamole plus aspirin did not meet predefined criteria for noninferiority compared with clopidogrel for the primary outcome of recurrent stroke across all patients in the PROFESS trial, and the relative difference between antiplatelet drugs was consistent across subgroups of patients with diabetes or obesity
Other medications	Clopidogrel plus warfarin: Low	Compared with Vitamin K antagonist alone (4.3%), risk of fatal and nonfatal bleeding was increased when combined with clopidogrel (12.3%) and clopidogrel plus aspirin (12.0%)
	Clopidogrel plus proton pump inhibitors: Insufficient for benefit-to-risk ratio; insufficient for cardiovascular effectiveness; low to moderate for gastrointestinal bleeding	<p>We found no eligible randomized controlled trials to assess whether concomitant use of a proton pump inhibitor increases the risk of cardiovascular events in patients taking clopidogrel</p> <p>Compared with nonuse, there was moderate-strength evidence that use of a proton pump inhibitor in average-risk patients taking clopidogrel (without aspirin) significantly reduced risk of hospitalization due to gastroduodenal bleeding</p> <p>There was low-strength evidence that proton pump inhibitor use does not significantly reduce composite risk of any gastrointestinal bleeding event either in average-risk or high-risk populations</p>
Genotype	Clopidogrel, prasugrel: Low	Compared with CYP2C19*17 noncarriers, carriers of the CYP2C19*17 allele did not have a significantly greater risk of major bleeding during treatment with clopidogrel
		Carriage of the ABCB1 3435 TT genotype also did not significantly impact the combined risk of major or minor bleeding in patients taking either clopidogrel or prasugrel

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

CONCLUSION

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

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

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