Oregon Health Resources Commission

Newer Antiplatelet Agents (AP)

Update # 1 Report

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Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In the winter of 2003 the Oregon Health Resources Commission (HRC) appointed a subcommittee to perform an evidence-based review of the use of Anti-Platelet drugs. Members of the subcommittee consisted of physicians, pharmacists, and other health care professionals. The subcommittee had 4 meetings. All meetings were held in public with appropriate notice provided.

Subcommittee members worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities.

Using standardized methods, the Southern California Evidence-based Practice Center (RAND) reviewed systematic databases, the medical literature, and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The RAND EPC's report, "Drug Class Review on Newer Antiplatelets" was completed in JULY 2005, circulated to subcommittee members, and posted on the web. The subcommittee met on September 26, 2005 to review the document and by consensus agreed to adopt the EPC report. Time was allotted for public comment, questions, and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the RAND EPC, the AP Subcommittee, or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the DHS.

The Standing Update Committee of the HRC revised this report based on the "Drug Class Review of Newer Antiplatelet Agents Update # 1" March 2007.

The full RAND EPC's draft report, *Drug Class Review on Newer Antiplatelets,* is available on the Office for Oregon Health Policy & Research, Practitioner-

Managed Prescription Drug Plan website:
http://egov.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon HRC and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website:
http://egov.oregon.gov/DAS/OHPPR/ORRX/HRC/process.shtml

You may request more information including copies of the draft report, minutes, and tapes of subcommittee meetings, from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

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There will be a charge for copying and handling in providing documents both from the Office of Oregon Health Policy & Research and from the Center.

Critical Policy:

- Senate Bill 819
  - "The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."

- Health Resources Commission
  - "Clinical outcomes are the most important indicators of comparative effectiveness"
  - "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Clinical Overview

Atherosclerosis often starts in late adolescence or early adulthood, and results in a variety of cardiovascular diseases (CVD) including ischemic coronary heart disease, stroke, and/or peripheral arterial disease (PAD). Ischemic coronary heart disease varies in its presentation and includes stable angina, unstable angina, non-ST segment elevated myocardial infarction (NSTEMI) and 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 (TIA) to thromboembolic stroke. Peripheral atherosclerosis frequently manifests as intermittent claudication of the lower extremity.

Definition of Antiplatelet Drugs

Although there are various approaches to secondary prevention of vascular disease, a principal component is the use of antiplatelet agents. Aspirin (ASA) has been considered the standard agent for many years. Numerous studies have shown the efficacy of ASA in reducing the occurrence of major cardiovascular events. In the past decade, newer antiplatelet agents have come to the forefront as adjuncts to or substitutes for ASA in certain clinical situations. However, their role is evolving and it is not always clear how best to utilize these drugs. This review evaluates the following newer antiplatelet agents in the context of secondary prevention of vascular disease:

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 Risk of a thrombotic event as follows: 1. Recent MI, Stroke, or established peripheral arterial disease (approved 11/97) 2. 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 without stent or CABG (approved 2/02) 3. For patients with ST-segment elevation acute myocardial infarction. (approved 8/06)	**X**		**X**	**X**
Ticlopidine (Ticlid)	**10/91**	1. To reduce the risk of thrombotic stroke (fatal or non-fatal) in patients who have experienced stroke precursors or a complete thrombotic stroke. 2. 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**

Quality of the Evidence

For quality of evidence the AP subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period, and the end points of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

1) Methods used for randomization
2) Allocation concealment and blinding
3) Similarity of compared groups at baseline and maintenance of comparable groups
4) Adequate reporting of dropouts, attrition, and crossover
5) Loss to follow-up
6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

1) Adequate description of the study population
2) Similarity of patients to other populations to whom the intervention would be applied
3) Control group receiving comparable treatment
4) Funding source that might affect publication bias.

Weighing the Evidence

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 body of evidence relevant to that question.

The subcommittee's task was to identify Newer Antiplatelet Drugs that would offer the greatest likelihood of success for the treatment of CVD including ischemic coronary heart disease, stroke, and/or PAD.

Scope and Key Questions

Key Question 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?**
Key Question 2	**For adults with acute coronary syndrome (ACS) or coronary intervention procedures (PCI), prior ischemic stroke or TIA, or symptomatic peripheral vascular disease do antiplatelets differ in safety or adverse events?**

Key Question 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?**

Summary of Results

Key Question 1a. In patients with ACS:

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?

One fair 6-month RCT compared ticlopidine and clopidogrel in patients with ACS who underwent angiography and found no significant difference in re-occlusion. This head-to-head trial reports intermediate outcomes only.

There was one good active-controlled trial (**CURE)** that compared clopidogrel 75mg + ASA vs. placebo + ASA. The trial involved 12,563 patients. The composite endpoint of CVA, nonfatal MI, or death from CV causes (MI, CVA) was modestly reduced for patients treated with clopidogrel ($p<0.001$, RR 0.82, ARR 2.1%, NNT=47). The endpoint of MI was also decreased ($p<0.001$, ARR=1.5%, NNT=67). The incidence of stroke or invasive vascular procedure failure was not significantly affected.

Key Question 1b. In patients with PCI:

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?

Five good to fair head-to-head trials were identified comparing aspirin taken in combination with clopidogrel and ticlopidine in patients undergoing PCI. There were no differences in major cardiac outcomes between the clopidogrel and ticlopidine groups within the first six months. However, when follow-up was extended to 27 months in one of the trials, all cause mortality and CV mortality were modestly lower in the ticlopidine group.

One good (**CLASSICS)** head-to-head trial compared clopidogrel plus ASA vs. ticlopidine plus ASA for effectiveness in patients with PCI. No difference was seen

between these two agents at 30 days for major adverse clinical events (death, MI, target lesion revascularization). Cardiovascular events (stroke, MI) and invasive procedure failure (PCI) were not reported in this trial.

Two good quality active-controlled RCTs evaluated the effects of pretreatment with loading doses of aspirin plus either clopidogrel 300 mg or placebo in patients undergoing revascularization procedures. In these trials, patients were followed for 8 and 12 (mean) months after revascularization. Results from both trials found that pretreatment with clopidogrel-plus-aspirin modestly reduced the composite risk of serious cardiovascular events compared to aspirin monotherapy. Absolute risk reductions were 3.4% and 3%, respectively. .

The good rated **CREDO** active-controlled trial reported the composite primary end-point of death, MI, stroke at 8.5% with clopidogrel compared to placebo 11.5% (RR 0.73) at one year. However at 28 days the composite endpoint of death, MI urgent target vessel revascularization failed to reach significance.

Key Question 1c. In patients with Stroke/TIA:

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?

There are no completed head-to-head studies comparing newer antiplatelet drugs for strokes or TIAs. There is an ongoing trial of 15,000 patients directly comparing ERDP/ASA with clopidogrel monotherapy for the prevention of recurrent stroke whose results are expected in 2008.

There were two good active-controlled trials: **ESPS-2** and **TASS.** The **ESPS-2** showed no difference in all cause mortality with ERDP + ASA vs. placebo + ASA. However there was a modest reduction of all strokes (p=0.006) at 24 months with ERDP + ASA as compared to ASA alone. Absolute risk reduction for all strokes was 3%. Neither trial evaluated Aggrenox® thus the evidence from these two studies does not correlate directly with options available in the US. The study used extended release dipyridamole (not available in the U.S.) in combination with variable doses of aspirin. TASS studied the effects of ticlopidine. We have not included results because of ticlopidine's unacceptable adverse event rates. (See Key Question 2)

With regard to secondary outcomes, ERDP/ASA was more effective than ASA at reducing combined stroke or TIA, as well as a variety of other vascular events. **ESPRIT** evaluated patients taking ASA with or without ERDP within 6 months of a TIA or minor stroke, and found that ERDP/ASA is slightly more effective than ASA alone in the prevention of new serious vascular events including the composite outcome of non-fatal stroke, non-fatal MI, non-fatal bleeding complication and death from all vascular causes.

Key Question 1d. In patients with PVD:

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?

There were no head-to-head trials comparing newer antiplatelet agents for patients with PVD. There was one good quality active-controlled trial **(CAPRIE)** of 29,000 patients that compared clopidogrel vs. ASA in predefined groups with mixed vascular disease over 1-3 years. In the **CAPRIE** PVD subgroup, 215 (6.7%) of 3223 patients in the clopidogrel group suffered a vascular event compared with 277 (8.6%) of 3229 patients in the ASA group. Treatment with clopidogrel did not reduce the risk of vascular death or death from any cause compared with treatment with ASA, but there was a small absolute benefit (NNT=87) in reducing the composite outcome of ischemic stroke, MI, and vascular death.

` **The AP Committee agrees by consensus that:**

1A. In patients with ACS:

- **Clopidogrel + ASA was modestly superior to ASA alone in reducing the combined endpoint of MI, stroke, CV death, or refractory ischemia**
- **The other AP drugs failed to show significant effects**

1B. In patients with PCI:

- **Long term administration of clopidogrel + ASA after PCI was associated with a lower rate of CV events including CV death, MI, or any revascularization.**

1C. In patients with stroke/TIA:

- **Combination of ERDP + ASA significantly reduced the incidence of non-fatal strokes, recurrent TIAs, and death compared to ASA alone. ERDP had a comparable effect to ASA. Aggrenox® was not studied. The study utilized sustained release dipyridamole (not available in the U.S.) combined with variable doses of aspirin.**
- **Combination of clopidogrel + ASA 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.**
- **Clopidogrel + ASA did not provide protection against MI in this population.**

1D. In patients with PVD:

- **Clopidogrel, the only AP drug studied, showed a reduction in the combined risk of ischemic stroke, MI, and vascular death.**

Key Question 2 For adults with ACS or coronary intervention procedures (PCI), prior ischemic stroke or TIA, or symptomatic peripheral vascular disease do antiplatelets differ in safety or adverse events?

Three metanalyses revealed that treatment with ticlopidine carried a significant risk of neutropenia when compared to ASA or clopidogrel. Rash and diarrhea were the most common reasons to stop ticlopidine as compared to clopidogrel.

Major bleeding (defined as disabling bleeding requiring at least two units of blood transfusion or intraocular hemorrhage) was significantly higher with increasing aspirin doses both in the placebo and clopidogrel groups. Minor bleeding (defined as other hemorrhages requiring interruption of the drug regimen) was significant with clopidogrel vs. placebo ($p<0.001$).

The most frequent overall adverse effects among patients taking ERDP + ASA were headache, dizziness, and GI symptoms. Withdrawals due to adverse effects of headache and diarrhea were higher in the ERDP/ASA than ASA arm of this trial.

Ticlopidine carries a black box warning concerning Neutropenia, thrombocytopenia, and aplastic anemia. It also has higher rates of rash than ASA or clopidogrel/ASA, but may be safter than ASA with regard to risk of GI bleeding.

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The AP Committee agrees by consensus that:

2. In adults with ACS, PCI, prior ischemic stroke or TIA, or symptomatic peripheral vascular disease, antiplatelets differ in safety and adverse events:

- **Ticlopidine should generally be avoided because of unpredictable adverse hematological effects, particularly neutropenia.**
- **Clopidogrel is as safe as ASA.**
- **The combination of clopidogrel + ASA has a higher risk of bleeding than ASA alone.**

Key Question 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?

No studies specifically compared the effectiveness of safety of the newer antiplatelet agents in acute coronary syndrome by patient age, gender, race, comorbidities, or concurrent medications. However, subgroup analysis did address some of these subgroups.

Age:
Two subset analyses from **CURE** and **ESPS-2** revealed no differences in results based on age.

Race:
Only one study that used ticlopidine in a primarily non-white population found no statistically difference between it and ASA in the prevention of recurrent stroke, MI, or PVD.

Gender:
One sub-set analysis and two active controlled trials failed to show a difference in efficacy or tolerability of newer antiplatelet agents.

Pregnancy:
There are no data available about the usage of the antiplatelet drugs in pregnancy.

Co-morbidities:
Both the CURE and PCI-CURE trials reported results for the diabetes subgroup (CURE included 2840 patients with diabetes). Although patients with diabetes had higher event rates than non-diabetic patients there was no difference in the primary outcome for patients treated with aspirin plus clopidogrel as compared to aspirin alone. The data for ERDP/ASA were significant for diabetics with prior stroke, as well as for patients with history of heart disease and PVD; all subgroups experienced similar stroke prevention benefits.

Other medications:
There are no head-to-head or active-control trials that address the question of newer anti-platelet agents given concurrently with other medications. Patients enrolled in the various trials were on a variety of medications including angiotensin-converting enzyme inhibitors (ACEIs), coronary vasodilators, diuretics, peripheral vasodilators, statins, β–blockers, calcium channel blockers (CCBs), platelet glycoprotein receptor inhibitors (GPIIb/IIIa), and antidiabetic agents. There was no evidence that concurrent use of these drugs leads to differential adverse consequences. However, all of the newer antiplatelet agents should be used cautiously with medications that increase the risk of bleeding.

The AP Committee agrees by consensus that:

3. In patient subgroups based on demographics (age, racial groups, gender), other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy is there one antiplatelet drug that is more effective or associated with fewer adverse events?

- **There are inadequate data available to determine whether there is a difference in efficacy or adverse effects between the newer antiplatelet agents for a particular age group, gender, or race.**
- **There are no data available about use of these drugs in pregnancy.**
- **Subsets of patients with diabetes, pre-existing CVD, and especially symptomatic PVD had a favorable response to these antiplatelet drugs.**
- **Further research is needed on PCI patients and the duration of treatment indicated with antiplatelet drugs.**

Conclusion

It is the decision of the AP Subcommittee that:

1. **In adult patients with ACS, PCI, or PVD. Clopidogrel + ASA is superior to ASA alone for reduction of cardiovascular endpoints including death, MI, and stroke.**
2. **In adult patients with stroke/TIA a combination of ERDP+ASA compared to ASA alone significantly reduces the combined endpoint of stroke, recurrent TIA, and death.**
3. **In adult patients with ACS, PCI, prior ischemic stroke or TIA, or symptomatic peripheral vascular disease, antiplatelets differ in safety or adverse events:**
    - **Ticlopidine should generally be avoided because of unpredictable adverse hematological effects, particularly neutropenia.**
    - **Clopidogrel is as safe as ASA.**
    - **The combination of clopidogrel + ASA has a higher risk of bleeding than ASA alone**
4. **There are inadequate data available to determine whether there is a difference between the newer antiplatelet agents for a particular age, gender, or race.**
5. **A weakness of this report is there was no data reported on patients with:**
    - **Chronic angina**
    - **Stents (either bare metal or drug-eluting)**
    - **Duration of treatment indicated with antiplatelet drugs for ACS or PCI.**
    - **Use of dipyridamole either in combination with aspirin or as monotherapy in formulations available in the U.S. .**

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Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.