

Chronic CAD & Antiplatelets: What's the Fit?

Platelets are essential to the thrombotic process that leads to myocardial infarctions



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Mr. Caw's query

Mr. Caw, 67, presents with a history of diabetes and hypertension. He is a former smoker, and he is in your office after being observed overnight in the emergency department (ED) due to complaints of chest pain. Subsequent investigations ruled out a myocardial infarct. Considering his risk factors, the ED physician suggested that Mr. Caw take acetylsalicylic acid 325 mg daily. Now, Mr. Caw is asking you if he really needs to take this medication.

For the answer, please go to page 49.

Mrs. Ingram's medication

Mrs. Ingram, 63, presents with hyperlipidemia. You are seeing her in your office one week after she was diagnosed with a non-ST elevation myocardial infarction. She was discharged on enteric coated acetylsalicylic acid (ASA) 81 mg, and clopidogrel 75 mg daily, as well as other cardiac medications. She is wondering for how long she needs to take ASA and clopidogrel.

For the answer, please go to page 49.

In this article:

- 1. What is the role of platelets in coronary artery disease?**
- 2. How are antiplatelet agents used in cardiovascular disease?**

The treatment of coronary artery disease (CAD) involves the practice of preventive cardiology, be it primary (preventing the first coronary event), or secondary (preventing subsequent myocardial infarctions (MI) or other vascular events). Currently, there are a number of medications that have proven beneficial in secondary prevention. Among them are antiplatelet agents, including acetylsalicylic acid (ASA), clopidogrel, ticlopidine, and dipyridamole. The purpose of this review is to outline the properties of each of these antiplatelet drugs, and to summarize the evidence for their use in cardiovascular disease, specifically CAD. Discussions about warfarin

and other anticoagulant agents are beyond the scope of this review.

What is the role of platelets in CAD?

The chronic process of progressive atherosclerosis has not been definitively linked with platelet function. However, platelets are essential to the thrombotic process that leads to MI. In an acute coronary syndrome, an atherosclerotic plaque becomes unstable and ruptures through the coronary arterial endothelial lining. This highly thrombogenic event causes platelet activation, a complex process involving a number of different molecules and pathways. The end result is the formation of a platelet plug, and subsequently a clot, which may manifest clinically as unstable angina (UA), non-ST elevation (NSTEMI), or ST elevation myocardial infarction (STEMI). Each antiplatelet agent has a different mechanism of action to inhibit specific activation processes. The end result is prevention of clot formation and, thus, acute MI or other cardiovascular events.

What is the role of ASA?

ASA acts as an antiplatelet agent by inhibiting the production of thromboxane A₂, a potent platelet activator and vasoconstrictor. A recent meta-analysis of antiplatelet trials in cardiovascular disease showed that ASA reduced the risk of non-fatal MI, stroke, or vascular death by 23% in patients considered high risk for

cardiovascular disease. High risk patients include those with documented CAD, cerebrovascular disease, or peripheral vascular disease (PVD).¹

ASA dosed from 75 mg to 325 mg daily is recommended for all patients post-MI, UA, or with chronic stable angina pectoris. These recommendations come from the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, and from the Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy.^{2,3}

The data for ASA use to prevent MI in patients without CAD is less conclusive since the relative benefit of ASA decreases as the cardiovascular risk of a patient decreases. The benefits that ASA offers may be offset by its risks in patients with no documented CAD or other cardiovascular diseases.

The ACCP recommends ASA only for patients over 50 who have at least one major risk factor for CAD.³ The U.S. Preventive Services Task Force recommends ASA be prescribed as primary prevention if a patient's five-year risk

Platelets are essential to the thrombotic process that leads to MI.

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Chronic CAD

of CAD is greater than 3%, as based on the Framingham Risk Profile.⁴ The www.med-decisions.com Web site provides a useful tool for calculating this risk. The American Diabetes Association recommends ASA for all diabetic patients over 30 who have at least one cardiovascular risk factor, including albuminuria.⁵

The major adverse effect of ASA is bleeding, specifically gastrointestinal (GI) and intracranial. Overall, the risk of intracranial and extracranial bleeding is < 1% per year. The risk of bleeding, especially GI, increases

proportionally with the dose of ASA. The odds ratio of patients being hospitalized with a GI bleed while taking ASA increased from 2.3 for a 75 mg daily dose to 3.9 for a 300 mg dose.⁶ Low-dose ASA use does not affect renal function, or blood pressure control.⁶

Clopidogrel is now commonly prescribed for patients post-PCI.

What is the role of clopidogrel?

Clopidogrel is a thienopyridine, which exerts antiplatelet activity by inhibiting adenosine diphosphate (ADP) mediated activation and aggregation of platelets. It is usually dosed 75 mg once daily. The first large trial involving

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Mr. Caw's resolution


Mr. Caw's five-year risk of having a cardiovascular event is greater than 20%, therefore, ASA 75 mg to 325 mg daily would be recommended.

Mrs. Ingram's case

Mrs. Ingram should be treated following the ACC/AHA guidelines based upon the CURE study. Therefore, we would recommend life-long ASA with at least nine months of clopidogrel.

clopidogrel was the Clopidogrel vs. Aspirin[®] in Patients at Risk of Ischemic Events (CAPRIE) study, conducted on patients with a previous history of ischemic stroke, MI, or symptomatic PVD.⁷ Patients were randomized to either clopidogrel 75 mg daily or ASA 325 mg daily. The annual risk of having either an ischemic stroke, MI, or vascular death was 5.32% in the clopidogrel arm and 5.83% in the ASA arm; there was a statistically significant relative risk reduction (RRR) of 8.7% with clopidogrel.

A more recent trial studied the use of clopidogrel in addition to ASA in patients with UA or NSTEMI: the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial.⁸ Patients were either randomized to receive ASA alone, or ASA with clopidogrel, dosed with an initial 300 mg load then 75 mg daily. Treatment duration ranged from three to 12 months, with a mean of nine months. The combined end point of MI, stroke, and cardiovascular death occurred in 9.3% of patients in the clopidogrel/ASA combination group, compared to 11.4% in the ASA-only group; there was a statistically significant 20%



LDL-C
39-60%
(type IIa and IIb)^{1†}

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Net Readings

1. American Heart Association:
www.americanheart.org
2. American College of Cardiology:
www.acc.org
3. The Heart.Org:
www.theheart.org
4. The Canadian Cardiovascular Society:
www.ccs.ca

RRR. This benefit was dampened by an increase in bleeding complications associated with the combination arm. Major bleeding occurred in 3.7% of the combination group versus 2.7% in the ASA-only group. As well, the incidence of minor bleeding occurred in 5.1% and 2.4% respectively. These differences were statistically significant.

Clopidogrel is now commonly prescribed for patients post-percutaneous coronary intervention (PCI), *i.e.*, coronary angioplasty with stent insertion. Two of the larger trials that used clopidogrel for this indication were PCI-CURE (a sub-study of CURE), and the Clopidogrel for the Reduction of Events During Observation (CREDO) trial.^{9,10} While PCI-CURE enrolled patients with acute coronary syndromes (ACS), CREDO involved patients with ACS and those having elective angioplasty. Both studies had patients on ASA and clopidogrel (or ticlopidine in PCI-CURE) for 28 to 30 days post-procedure. They were then randomized to ASA alone, or ASA with clopidogrel, for up to one year. In PCI-CURE, the incidence of the combined end point of cardiovascular death, MI, or urgent revascularization was 4.5% in the combination arm, and 6.4% in the ASA-only arm; there is a sta-

tistically significant 30% RRR with clopidogrel in addition to ASA. In CREDO, the combined end point of death, MI, or stroke at one year occurred in 8.5% of patients in the clopidogrel/ASA group, and 11.5% in the ASA alone group; a statistically significant RRR of 26.9%.

The current ACC/AHA guidelines recommend clopidogrel therapy be combined with ASA for all patients with UA or NSTEMI, regardless of whether early PCI is planned. This combination therapy should continue for at least one month, and up to nine months for patients post-PCI, while those patients post-UA/NSTEMI should continue for up to nine months. For patients with chronic stable angina, clopidogrel is recommended only if ASA is contraindicated or not tolerated.^{2,3}

Reports of neutropenia or thrombocytopenia, including thrombotic thrombocytopenic purpura (TTP), have been described with clopidogrel, but the incidence has not been as high as with ticlopidine. Most of the adverse effects reported in the large clinical trial data of clopidogrel are related to bleeding complications.^{7,8} From the CAPRIE study, rash and diarrhea were the only side-effects more common in the clopidogrel patients than in the ASA group.⁷

What is the role of ticlopidine?

Ticlopidine is a thienopyridine, like clopidogrel, and thus exerts antiplatelet activity via the same mechanism of action. It is dosed at 250 mg twice daily. Unlike clopidogrel, ticlopidine has not been the focus of large trials. This may be related to its delayed antithrombotic effect, and to its side-effect profile. Given at its usual dose, it may take up to two

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Take-home message

A number of medications have proven beneficial in secondary prevention. ASA, clopidogrel, and ticlopidine are among them.

- ASA acts as an antiplatelet agent by inhibiting the production of thromboxane A₂, a potent platelet activator and vasoconstrictor.
- Clopidogrel is a thienopyridine, which exerts antiplatelet activity by inhibiting adenosine diphosphate (ADP) mediated activation, and aggregation of platelets.
- Ticlopidine is a thienopyridine, like clopidogrel, and thus exerts antiplatelet activity via the same mechanism of action.

weeks before adequate protection is achieved.⁶ Nevertheless, both the ACC/AHA and ACCP guidelines recommend the use of ticlopidine for patients with UA or NSTEMI when ASA is not tolerated.^{3,11} Ticlopidine can be used in addition to ASA for patients post-PCI for one month. Since clopidogrel is recommended for the same indications, and given its better safety profile, clopidogrel has become the preferred thienopyridine.

The concern about the safety profile of ticlopidine has prevented it from becoming more prominent, compared to clopidogrel. The most frequent adverse effect, other than bleeding, is neutropenia (2.4% incidence), while the risk of severe neutropenia or agranulocytosis is about 0.8%. There are also reported cases of aplastic anemia and thrombocytopenia, including TTP. The reported risk of TTP is estimated at about



Lipid levels should be monitored periodically and, if necessary, the dose of LIPITOR adjusted based on target lipid levels recommended by guidelines.

Caution should be exercised in severely hypercholesterolemic patients who are also renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently.


The effects of atorvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol on cardiovascular morbidity, mortality, or total mortality have not been established.

† A patient-year represents the total time of exposure to LIPITOR as defined by the sum of each patient time on LIPITOR.⁵

Chronic CAD

0.02%, this is compared to 0.0004% in the general population.⁶

What is the role of dipyridamole?

Dipyridamole exerts its antiplatelet effect differently from both ASA and the thienopyridines, although its exact mechanism is uncertain. Given its vasodilatory effects, it may induce ischemia by a coronary steal mechanism, and hence its role in nuclear myocardial perfusion scanning to provoke ischemia. Due to this effect, neither the ACCP or ACC/AHA guidelines recommend dipyridamole for patients with CAD and angina.^{2,3} Dipyridamole in combination with ASA is recommended for patients post-ischemic cerebrovascular events to prevent recurrent strokes.¹² 

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See page 31 for Frequently Asked Questions on chronic CAD and antiplatelets.