Antithrombotic options

We currently have a variety of antithrombotic agents for prevention in cardiac care: acetylsalicylic acid (ASA), an irreversible cyclooxygenase-1 (COX-1) inhibitor; dipyridamole, a phosphodiesterase inhibitor; clopidogrel and ticlopidine, both thienopyridines; and warfarin, an inhibitor of vitamin K-dependent coagulation factor synthesis. Oral thrombin inhibitors are in Phase III trials and have the advantage of not requiring monitoring.

This article will consider the preventive antithrombotic care in several case scenarios of a woman with escalating cardiovascular risk. We will examine the benefits and risks of some of the different types of antithrombotic medications in the treatment of hypertension, Type 2 diabetes, chronic atrial fibrillation (AF), and congestive heart failure (CHF). We will also look at the effectiveness of antithrombotics as second-line treatment after a myocardial infarction (MI).
Case: Age 55 with hypertension

A 55-year-old woman visits our clinic for hypertension. She has no history of coronary artery disease, stroke, or peptic ulcer disease. She has no allergies, but has smoked one pack of cigarettes per day for the past 20 years. Her current medications are ramipril and hydrochlorothiazide. Her blood pressure is 136/74 mmHg and her body mass index is 22. Her total cholesterol is 5.2 mmol/L and her high-density lipoprotein cholesterol is 1.0 mmol/L.

Should acetylsalicylic acid therapy be recommended? See discussion below.

Case discussion age 55: Primary prevention

What is the benefit of ASA in primary prevention?

While four of the five large randomised, controlled primary prevention trials found ASA decreases the risk of MI, there is still some debate about the use of ASA for primary prevention (Tables 1 & 2).

First, it decreases non-fatal MI without affecting overall mortality. Some have suggested that ASA may simply mask the presentation of MI. Second, ASA increases the risk of hemorrhage, either gastrointestinal or intracranial. Third, the effect of ASA is small and the treatment period is long. When a patient’s five-year risk of coronary event has been calculated at 5%, ASA reduces that risk by just 0.3%. A recent meta-analysis showed that the use of ASA in low-risk patients avoided only four events per 1,000 patients treated for five years. The key point is that the benefit of ASA is dependent on the baseline risk of cardiovascular events. The U.S. Preventive Services Task Force recommends consideration of ASA for primary prevention when the five-year risk of coronary artery disease is 3% or more.

What is the five-year risk of a cardiovascular event for our patient?

The five-year risk of an event can be calculated based on the Framingham Heart Study or by simply reducing the National Institute of Health (NIH)-calculated 10-year risk by half. Visit the NIH Web site at http://www.nih.gov for more details.

In our case presentation, we calculated our patient’s five-year risk of a cardiac event by

Table 1

<table>
<thead>
<tr>
<th>10-year risk (%)</th>
<th>5-year risk (%)</th>
<th>CV events prevented per 1,000 patients</th>
<th>GI bleeding caused per 1,000 patients</th>
<th>Hemorrhagic strokes caused per 1,000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>1-4</td>
<td>2-4</td>
<td>0-2</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2-8</td>
<td>2-4</td>
<td>0-2</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>4-12</td>
<td>2-4</td>
<td>0-2</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>5-16</td>
<td>2-4</td>
<td>0-2</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>6-20</td>
<td>2-4</td>
<td>0-2</td>
</tr>
</tbody>
</table>

CV: cardiovascular  
GI: gastrointestinal

### Table 2

**Randomised, controlled trials of ASA for primary prevention**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Blinding</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Male Doctors’ Trial [30]</td>
<td>N=5,139 Male physicians</td>
<td>No</td>
<td>ASA</td>
<td>No reduction in the risk of death from any cause or in the risk of stroke.</td>
</tr>
<tr>
<td>Physician’s Health Study [11]</td>
<td>N=22,071 Male physicians</td>
<td>Yes</td>
<td>ASA, 325 mg every other day vs. placebo</td>
<td>Reduction in the occurrence of MI by 44%. Stopped prematurely based on reduction in nonfatal and fatal MI, but excluded sudden deaths.</td>
</tr>
<tr>
<td>Thrombosis Prevention Trial [31]</td>
<td>N=2,540 Males at high CAD risk</td>
<td>Yes</td>
<td>ASA and low-dose warfarin</td>
<td>Reduction in MI. No reduction in death from any cause or in the risk of stroke.</td>
</tr>
<tr>
<td>Primary Prevention Project [32]</td>
<td>N=4,495 ≥ 1 major CAD risk factor</td>
<td>No</td>
<td>ASA, 100 mg daily vs. none</td>
<td>Reduction in occurrence of MI. Reduced major cardiac events from 8.2% to 6.3%. Bleeding higher (1.1% vs. 0.3%) with 1 fatal bleed per 8,000 patient-years. No reduction in death from any cause or in the risk of stroke.</td>
</tr>
<tr>
<td>Hypertension Optimal Treatment Study [12]</td>
<td>Males &amp; females with hypertension</td>
<td>Yes</td>
<td>ASA, 75 mg daily</td>
<td>Reduction in occurrence of MI. No reduction in death from any cause or in the risk of stroke.</td>
</tr>
</tbody>
</table>

The annual risk of cardiovascular disease was low and ranged from 0.4% to 1.2%.

ASA: acetylsalicylic acid  
MI: myocardial infarction  
N: number of participants in study  
CAD: coronary artery disease
going to the NIH Web site and entering her specifics in a table. We logged her age, sex, smoking status, total cholesterol, high-density lipoprotein cholesterol, and systolic blood pressure. Her five-year risk is then calculated to be 4%.

Do the results of primary prevention studies apply to women?
These five large randomised, controlled trials enrolled mostly middle-aged men (Table 2). Only two studies, the Hypertension Optimal Treatment Study (HOT) and the Primary Prevention Project (PPP) included women. In a recent meta-analysis for high-risk patients, reductions in vascular events were separately statistically significant in men and women.6 The non-randomised Nurses’ Health Study found, during a six-year followup, that the combined end point of nonfatal MI and fatal coronary artery disease was lower for patients taking ASA (one to six tablets per week). For women over age 55, ASA use was associated with a lower rate of coronary artery events (112 versus 165 per 100,000 person-years of followup). For stronger evidence about primary prevention in low-risk women, we await the Women’s Health Study.7

What about ASA and hypertension?
The benefit of ASA therapy may be less apparent in hypertensive patients. The HOT trial examined ASA in patients with treated hypertension. In high-risk patients (≥ 3% annual risk

About the authors ...
Dr. Biem is staff member, division of general internal medicine at the Royal University Hospital, University of Saskatchewan, Saskatoon, Saskatchewan.

Dr. Wilson is staff member, division of general internal medicine at the Royal University Hospital, and professor and head of pharmacology, University of Saskatchewan, Saskatoon, Saskatchewan.
of vascular event), reductions in vascular events occurred in both hypertensive and normotensive patients.\(^6\)

ASA also decreases production of vasodilator prostaglandins. Subgroup analyses of randomised, controlled trials suggest ASA may counteract the beneficial hemodynamic effects of angiotensin-converting enzyme (ACE) inhibitors; however, clinical importance of this effect is uncertain.\(^8\)

For our patient, ASA would be recommended for primary prevention after her hypertension is controlled. There could be risk of bleeding, however, the effect of dosage on this risk is unclear. Because of the concern of intracranial hemorrhage, some guidelines recommend 75 mg of ASA per day for patients with hypertension.\(^9\) The 81 mg tablet available in Canada is a reasonable choice.

**Case discussion age 60: Primary prevention in the higher-risk patient**

What about ASA and diabetes?\(^\)

Diabetics have an annual risk of vascular events of over 3% per year.\(^{10}\) The risk of vascular events may be as high for middle-aged diabetics as it is for non-diabetics with coronary artery disease.\(^{10}\)

In a subgroup of the Physician’s Health Study, the risk of vascular events in diabetics was halved with ASA.\(^{11}\) A subgroup of the HOT trial showed that in 1,501 diabetics, ASA decreased the risk of all cardiovascular events by 15% and the risk of MI by 36%.\(^{12}\)

The 1998 Canadian Clinical Practice Guidelines for the Management of Diabetes recommended that ASA be considered for primary prevention in diabetics over age 30.\(^{13}\) The American Diabetes Association recommends ASA in diabetics with additional cardiovascular risk factors, such as obesity, smoking status, and a family history of cardiovascular disease.\(^{14}\)

**Case: Age 65 after myocardial infarction**

Our patient, now 65, comes to our clinic after a recent admission for a non-Q wave myocardial infarction (MI) complicated by recurrent chest pain and having been treated with two-vessel angioplasty. She has no symptoms of congestive heart failure (CHF), but an echocardiogram (ECG) shows an ejection fraction of 45%. Her medication list has grown to include ASA, clopidogrel, and metoprolol.

See discussion below.

**Case discussion age 65: Secondary prevention after MI**

What is the role of antiplatelet therapy for secondary prevention after MI?\(^\)

For those without contraindications, patients with established occlusive vascular disease benefit from antiplatelet therapy. Among 20,000 patients with previous MI, the absolute risk...
reduction is 4% with two years of ASA therapy compared to control. In a recent meta-analysis considering high-risk patients, there were reductions of about one-third in non-fatal MI, one-third in non-fatal stroke, and one-sixth in vascular death. There was no evidence that non-vascular deaths were increased, suggesting mortality was significantly reduced in high-risk patients.

In secondary prevention, the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial randomised 12,562 patients after unstable angina and non-Q wave MI to either a combination of ASA, 75 mg, and clopidogrel, or ASA alone. The composite end point (death, MI, stroke) was reduced to 9.3% from 11.4%. There was an absolute increase of 1% in bleeding. However, there was no difference in severe bleeding.

Another recent study, the Percutaneous Coronary Intervention (PCI)-CURE trial, showed that a combination of clopidogrel and ASA was better than ASA alone after percutaneous coronary intervention for acute coronary syndromes.

Because most trials lasted only a few years, the duration of therapy for secondary prevention is uncertain.

What about patients who are intolerant to ASA?

Some patients are allergic to ASA. Some have gastrointestinal intolerance or peptic ulcer disease. The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial randomised 19,185 patients with a history of recent stroke, MI, or symptomatic peripheral arterial disease, comparing treatment with clopidogrel to that with ASA. Within the one- to three-year followup period, cardiac events were reduced from 5.8% to 5.3%. Because clopidogrel is only marginally more effective than ASA, and because it costs more, ASA is recommended as first-line therapy.

Lipid levels should be monitored periodically and, if necessary, the dose of LIPICTOR 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 LIPICTOR as defined by the sum of each patient time on LIPICTOR.
What about warfarin after MI?
There have been several large studies of anticoagulants alone and in combination with antiplatelet agents for post-MI treatment. In the Warfarin on mortality and Reinfarction after MI Study (WARIS), 1,214 patients post-MI were randomised to treatment with warfarin or placebo for an average of 37 months. Patients treated with warfarin had fewer reinfarctions and strokes.18

In the Coumadin Aspirin Reinfarction Study (CARS), 8,803 patients were randomised to either ASA, 160 mg; warfarin, 3 mg, with ASA, 80 mg; or warfarin, 1 mg, with ASA, 80 mg. The primary end point was a first occurrence of reinfarction, non-fatal stroke, or cardiovascular death. Patients were followed for 33 months. Low-dose warfarin was no more effective than ASA alone.19

The Combination Hemotherapy And Mortality Prevention (CHAMP) study randomised 5,059 patients within two weeks of MI to either ASA, 162 mg, or ASA, 81 mg, and warfarin. There was no difference in cardiovascular mortality, but there was an increase in bleeding.20

The Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT) 2 trial randomised patients after thrombolysis to either warfarin with ASA, or ASA alone. Patients had a followup angiogram at three months. The reocclusion rate was 18% for those given combination therapy compared to 30% for those who used ASA alone. Event-free survival was better with the combination.21

In the multicentre open label WARIS-II trial 3,630 were randomised to ASA, 160 mg; warfarin; and ASA, 75 mg, with warfarin. After a mean followup of four years, the primary outcome (a composite of death, nonfatal reinfarction, or thromboembolic cerebral stroke) occurred in 20% with ASA, 16.7% with warfarin, and 15% with the combination. Major, nonfatal bleeding was observed in 0.62% of patients per treatment-year in both groups receiving warfarin and in 0.17% of patients receiving ASA. Warfarin, in combination with ASA or given alone, was superior to ASA alone.22

If our patient takes warfarin and ASA in combination, the challenge is to meticulously manage the warfarin anticoagulation. The warfarin trial results were obtained under ideal circumstances of randomised, controlled trials, which may not translate into clinical practice.

Case: Age 70 with CHF and atrial fibrillation

Now 70, our patient complains of palpitations and shortness of breath. On auscultation, she has a systolic murmur and crackles at the lung bases. ECG shows atrial fibrillation, a left atrial thrombus, and an ejection fraction of 35%.

See discussion below.

Case discussion age 70: CHF and AF

What is the evidence for antiplatelet therapy and warfarin in CHF?
A recent meta-analysis of long-term randomised, controlled trials found no benefit of antiplatelet agents or anticoagulants for patients with CHF in sinus rhythm.23 In the Warfarin-Aspirin Study of Heart failure (WASH), 279 patients with CHF were randomised to ASA, warfarin, or neither. There was an increase in hospitalisation for CHF in the group taking ASA.24 This study was not powerful enough to show a difference in mortality and was a pilot study for the ongoing Warfarin and Antiplatelet Therapy study in Chronic Heart failure (WATCH), which ran-
domises 4,500 patients to warfarin, ASA, or clopidogrel.

**What is the evidence for warfarin therapy in AF?**

About 5% of patients over age 65 have AF.\(^{25}\) Warfarin and ASA both reduce the risk of cardioembolic stroke from AF by approximately 65% and 20% respectively.\(^{26,27}\)

A recent patient level meta-analysis of six trials comparing warfarin versus ASA for treatment of AF showed that the risk of bleeding was 2.2 events with warfarin versus 1.3 events in control per 100 patient-years. Treating 1,000 patients for one year would prevent 23 ischemic strokes, while causing nine additional bleeds. There was no difference in all-cause mortality.\(^{28}\)

**Should our patient take warfarin alone or combine it with ASA?**

Based on a recent trial showing that warfarin was effective in reducing coronary events, warfarin therapy alone is probably as effective as combined therapy, but with less risk of bleeding. Combined therapy has a higher risk of bleeding.\(^{29}\)

---

**Case Summary**

We have discussed evidence applicable to decision-making about antithrombotic therapy for a female with various levels of cardiovascular risk.

This patient has had increasingly strong indications for outpatient antithrombotic therapy, as her cardiac care has moved from primary prevention to secondary prevention, and finally, to the management of CHF and AF.

---

**Take-home message**

- The baseline cardiovascular event risk determines the benefit of preventive antithrombotic therapy.
- ASA should be considered when the five-year risk of cardiovascular events is ≥3%.
- Diabetics may have as high as 3% risk per year of cardiovascular events.
- Warfarin is more effective than ASA alone for secondary prevention of cardiovascular events in patients with MI, but has a higher risk of bleeding.
1998; 159 Suppl 8:S1-29.


