

# Reducing CV Risk: What Works?

Many pharmacologic and non-pharmacologic therapies in the arsenal of cardiac prevention have been shown to attenuate cardiac risk in selected groups of patients. But who should receive what therapy? How do you decide?

Sarah A. Ramer, BSc, MD, FRCPC and Jafna L. Cox, BA, MD, FRCPC, FACC

During the past two decades, an impressive arsenal of therapies has been developed to prevent first (primary prevention) or further (secondary prevention) ischemic cardiac events. Whereas 20 years ago, a patient at risk for ischemic heart disease might expect to take “an aspirin a day,” in the modern era an asymptomatic patient might be prescribed up to five or six different medications in order to attenuate their long-term risk of a cardiac event.

Which weapons

are most effective, and for what patients? In this world of evidence-based medicine, it is becoming more and more difficult for primary-care providers to sift through the increasingly large quantities of published data to get to the heart of the matter: What therapies should be prescribed to reduce the risk of a cardiac event?

Many such patients come into their physician's office asking how best to avoid a first heart attack. The first steps are to determine what other risk factors the patient may have and to elicit any symptoms of occult or manifest heart disease. The question then becomes: How is this patient best treated?

## ASA

Since the publication of the Physician's Health Study in 1989,<sup>1</sup> acetylsalicylic acid (ASA) has been a widely accepted primary-preventative measure for male patients at risk for a first heart

attack. In four other large clinical trials, it was found that ASA reduces the risk of a first cardiac event by about one-third.<sup>2</sup> In the primary-prevention setting, however, the potential risks of ASA must also be considered, since the absolute risk of a cardiac event is relatively low. One meta-analysis found that ASA reduced all CV events by 15% and myocardial infarction (MI) by 30%, but with a significant 69% risk of bleeding complications.<sup>3</sup> When adverse effects were considered, ASA therapy was worthwhile only when the coronary event risk was 1.5% per year.

The beneficial effects of ASA in primary prevention of female patients are less clear than in men. The Women's Health Study, the largest trial of ASA for primary prevention in women, randomly assigned healthy women, ages 45 or older, to receive ASA or placebo on alternate days.<sup>4</sup> After a mean followup of 10.1 years, ASA had no effect on

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the risk of MI or on death from CV causes, but significantly increased the risk of gastrointestinal bleeding requiring transfusion. In a subgroup analysis, ASA reduced the risk of MI only in women ages 65 and older.

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### *Clopidogrel*

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Clopidogrel has not yet been studied in primary prevention of CV events, but a large, randomized trial is currently underway.<sup>5</sup>

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### *Beta-blockers*

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Blood pressure (BP) lowering with a variety of agents has been shown to decrease CV risk. In a large clinical trial, beta-blocker therapy has been associated with a significant reduction in the risk of a first non-fatal MI among hypertensive patients.<sup>6</sup> Currently, however, the American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines do not strongly support the use of beta-blockers as initial therapy in patients without a history of MI (Class IIa recommendation).

patients at high risk of a cardiac event, demonstrated decreased rates of CV death, non-fatal MI, stroke and new-onset diabetes. The subsequent European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) trial compared perindopril to placebo in a group of patients with a known history of stable coronary artery disease but who were, overall, at lower risk than the HOPE population. There was a significant decrease in the combined endpoint of non-fatal MI, CV death or CV arrest in the perindopril treatment arm, but no significant benefit was found among patients without a history of prior MI.

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### *Statins*

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Six major studies have examined the role of statins in primary prevention, and each of these trials showed benefit in the treatment group. In the earlier trials, this benefit was driven by a significant decrease in CV events, while in some later studies, a mortality benefit was also shown.

For example, the West of Scotland Coronary Prevention Study demonstrated significant relative risk reductions in cardiac death (32%) and all-cause mortality (22%) in male patients with hypercholesterolemia. The Air Force/Texas Coronary Atherosclerosis Prevention Study, the first primary prevention study to include women, demonstrated, after 5.2 years of followup, significant decreases in rates of first cardiac events and the need for revascularization in the lovastatin group.

*ASA reduced the risk of MI only in women ages 65 and older.*

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### *ACE inhibitors/ARBs*

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ACE inhibitors are well-established as an effective means of reducing CV risk among hypertensive patients.<sup>7,8</sup> Angiotensin II receptor blockers (ARBs) have shown to be particularly effective among hypertensive patients with diabetes.<sup>9</sup> Current evidence also indicates a protective effect of ACE inhibitors among some higher risk patients with or without a history of hypertension. For example, the Heart Outcomes Prevention Evaluation (HOPE) trial,<sup>10</sup> which examined the effects of ramipril in

#### **About the authors...**

**Dr. Ramer** is the Chief Cardiology Resident, Dalhousie University, Halifax, Nova Scotia.

**Dr. Cox** is the Director of Research, Division of Cardiology, and a Professor, Departments of Medicine and Community Health and Epidemiology at Dalhousie University and a Staff Cardiologist at the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia.



Case 2: Roberta, 76, has a history of hypertension and hypercholesterolemia. She presents with small, uncomplicated non-ST-elevated MI (NSTEMI). A stress MIBI pre-discharge reveals a small, fixed defect; she denies chest pain with exertion.

Roberta's scenario is also common. She is at significant risk for a subsequent CV event given her age and history of heart disease, but she is asymptomatic. What therapies should she be offered?

### ASA

Data from the Antithrombotic Trialists' Collaboration indicate clear benefits of ASA over placebo in patients with unstable angina, acute MI or prior MI. The absolute risk reductions in various trials range between 5% and 10%, with numbers needed to treat resultantly as low as 10 patients to prevent one recurrent cardiac event. The benefit of ASA in this clinical situation is clear and it should only be withheld if a significant contraindication to ASA therapy exists.

*In secondary prevention trials, beta-blockers reduced the odds of death by 23%.*

### Clopidogrel

Based on the results of the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, patients with unstable angina or NSTEMI in many centres are treated with clopidogrel (a 300 mg loading dose followed by 75 mg/day) in addition to ASA. In CURE, clopidogrel was continued for nine to twelve months, resulting in a significant reduction in a composite endpoint of death from CV causes, non-fatal MI or stroke (relative risk reduction 80%; absolute risk reduction 2.1%). Some physicians recommend continuing

clopidogrel beyond one year or even indefinitely, as long as the drug is well-tolerated and expense is not an issue. This approach is primarily considered for patients with more severe vascular disease (e.g., prior MI or cerebrovascular event or peripheral vascular disease).

### Beta-blockers

Beta-blockers are a standard of care for secondary prevention among patients with no contraindications to this therapy. In a systematic review, the overall mortality in 31 long-term trials that included almost 25,000 patients was 10.1%; beta-blockers reduced the odds of death by 23%.

### ACE inhibitors/ARBs

Several studies have demonstrated a benefit of ACE inhibitor therapy begun within 24 hours of an MI, particularly in subgroups with large anterior MIs or with congestive heart failure. The use of ARBs in patients with a large MI complicated by heart failure has also been shown to be of benefit, though not superior to ACE inhibitors and potentially harmful when used in combination. ARBs in this setting should therefore be considered as an alternative therapy for patients intolerant of ACE inhibitors and should not be used as add-on therapy.

The role of ACE inhibitors or ARBs in smaller, uncomplicated MIs among patients with preserved left ventricular systolic function is less clear. Results from HOPE, EUROPA and the Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE) trial<sup>10</sup> suggest secondary prevention with ACE inhibitors is only necessary for patients at the highest risk.

### Statins

The role of cholesterol lowering with statins in secondary prevention of cardiac events is well-established and supported by robust data from a number of large, randomized clinical trials. The cardioprotective effects of statin therapy correlate in a linear fashion with the degree of low density lipoprotein (LDL) lowering; however, this class of medication has also been shown to

have pleiotropic effects that contribute to the observed improved outcomes. For example, the mortality benefit of simvastatin compared to placebo in the Scandinavian Simvastatin Survival Study was highly significant (8% vs. 12% total mortality at the end of 5.4 years); similar reductions were seen in other large trials.


Based on early studies, previous published

guidelines recommended an LDL target of less than 2.5 mmol/L in patients with established coronary disease or diabetes. Based on emerging evidence, however, lower levels of LDL confer additional benefit, with improved outcomes seen even among patients with an average LDL less than 2.0 mmol/L, compared to those patients with an average close to previous guideline levels.

### Other therapies

Non-pharmacologic therapies, such as exercise, dietary modification and even the moderate use of alcohol, have also been associated with decreased rates of CV events. Smoking cessation is also extremely important, with a substantial drop in CV risk after even one year of quitting.

The putative benefits of vitamins C and E in CV prevention have been based on observational data that patients who consume more vegetables (high in antioxidants) have lower rates of CV disease. Large randomized, controlled trials, however, have failed to demonstrate the benefit of these antioxidant therapies.<sup>10</sup>

For many years, epidemiologic data has supported a hypothesis that fish consumption correlates with reduced CV risk. This benefit appears to relate to changes in lipid profile, as well as to modification of the interaction of platelets with the vascular endothelium. The *Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Prevenzione* trial found a significant reduction in a combined endpoint of death, non-fatal MI and stroke among patients with recent MI who were treated with fish-oils (n-3 polyunsaturated fatty acids), compared to placebo. 

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