Secondary Prevention

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The past 20 years have witnessed dramatic changes in our understanding and treatment of ischemic heart disease. In terms of management, two major trends, defining two categories of cardiologists, have emerged. The first is the fast-growing predilection for the invasive approach to coronary artery disease, epitomized by surgical or interventional reperfusion, both in the acute setting (primary angioplasty) and in the stable phase. Those who embrace this strategy are known as interventional cardiologists, and are engaged in what in effect is a sophisticated form of “plumbing.” They are unrepentant technophiles, always on the lookout for the most up-to-date type of stent and the latest devices bristling with electronics. In stark contrast to this first category is the preventive cardiology approach. This is based on the rationale that intervention only takes care of a discrete manifestation of the disease, but fails to address the possibility that atherosclerosis may progress to another vessel or wreak havoc again in the same vessel that has been subjected to angioplasty or bypass surgery. It has been said that the preventive cardiologists would dearly love to ban their plumber colleagues from plying their trade. They are intent on understanding the intimate mechanisms that lead to the initiation and progression of atherosclerosis in the coronary arteries and on devising pathophysiologically based treatments. Not only do these two categories of cardiologists differ in their therapeutic strategies, they also differ in that the interventional cardiologist is seemingly more remote and spends only minimal time with patients outside of the operating theater, whereas the preventive cardiologist is more interactive and never tires of sharing advice and ideas with his or her patients.

Much skepticism was harbored against preventive cardiology in the past. Any doubts have now been cast aside thanks to the advent of evidence-based medicine, which has provided ample proof of the efficacy of this approach. Skepticism has also receded as drugs both old and new have been proven to prevent the progression and even the onset of atherosclerosis. Thus, angiotensin-converting (ACE) enzyme inhibitors, statins, antiplatelet agents, anticoagulants, and β-blockers have had their therapeutic profile changed or enhanced by studies—some of them megatrials—proving their benefit in secondary prevention. Some of these trials were especially rewarding in that they...
provided findings that were totally unexpected. We have learned, for instance, that statins play an important role even when low-density-lipoprotein (LDL) cholesterol levels are normal. Likewise, some ACE inhibitors are of benefit even when the blood pressure is normal. This in turn has given rise to a spate of questions and new concepts concerning the mechanisms of action of these drugs. It is being increasingly hypothesized that these recently recognized benefits stem not from the primary pharmacological property of the drug (e.g., reduction in blood pressure for the ACE inhibitors, reduction in cholesterol levels for the statins, reduction in heart rate and blood pressure for the \( \beta \)-blockers), but from secondary and possibly equally important mechanisms of action converging on the vascular endothelium. This fascinating concept has breathed new life into the curious term “pleiotropism.” Although few appear to know the exact meaning of the word and isolated voices even question its relevance, it denotes the fact a single drug is endowed with several mechanisms of action—by analogy with the genetic definition of the term. An intriguing conclusion drawn from the trials referred to above is that, as far as secondary prevention is concerned, it is more important for a drug to be included as part of the patient’s treatment program than to specify just exactly how it should be used. As these drugs are to be used even when their primary pharmacological target is normal, it follows that we cannot adjust the dose according to their action. This has given rise to the controversial debate on the virtues of an ideal polypill that would combine all the agents with proven benefit in secondary prevention—which, in addition, would greatly enhance compliance.

In this issue of *Dialogues* devoted to secondary prevention, the authors have given pride of place to the available pharmacological tools, but it is important to remember that the first step in secondary prevention is to improve our patients’ lifestyle. Although this topic has been addressed in previous issues of *Dialogues*, let us be here once more reminded how vital it is to spend time with our patients and explain the importance of stopping smoking, eating a healthy diet, engaging in regular exercise, and controlling diabetes and, of course, blood pressure.

Our final word will be to point out that for all the opposition between the interventional approach and the preventive approach, it is not a matter of “one or the other” but of “both together”: only when both approaches dovetail to form a single therapeutic strategy will we be truly successful in our fight to curb the damage inflicted by coronary disease.
For most populations in the world, the last 100 years have witnessed greater improvements in health status, compared with any other time in history. Globally, life expectancy increased by about 25 years during the twentieth century, with a greater than 50% increase in longevity for most populations. These improvements in health are likely a result of both improvements in disease prevention and health care as well as improvements in socioeconomic conditions in most societies. During this period, the major causes of death and disability have shifted from a predominance of nutritional deficiencies and infectious diseases to chronic diseases such as cardiovascular diseases (CVD), cancers, and diabetes. Most Western countries (such as those in North America and Western Europe) exhibited this epidemiological transition in the first half of the twentieth century, resulting in marked increases in CVD during the first half of the century.

Cardiovascular diseases (CVD) are the major cause of death and a significant cause of disability in the Western world and are now threatening to impose an increasing health burden on developing nations. People with preexistent vascular disease are those at highest risk for adverse cardiovascular outcomes and require aggressive secondary preventive therapies. Large strides have been made in the development of pharmacologic agents that target atherogenesis, thus offering the ability to greatly impact on disease progression and to prevent events. Compelling data from randomized controlled trials have shown the benefits of aspirin (or antiplatelets) and angiotensin-converting enzyme (ACE) inhibitors (A), β-blockers and blood pressure-lowering agents (B), and cholesterol-lowering agents (C), particularly statins, in preventing recurrent events and improving survival. These data are the foundation for the advice for secondary prevention—the ABCs. In addition, the evidence for the central role of lifestyle factors as determinants of risk has led to increased efforts toward developing interventions aimed at modifying lifestyle patterns. Today’s biggest challenge is one of implementation. Our focus should turn to educating physicians and patients alike about available therapies and their indications and potential benefits. In addition, systematic, sustainable, and globally applicable approaches to the secondary prevention of CVD need to be developed to truly realize the vast benefits of existing therapies.

Keywords: cardiovascular disease; cardiovascular prevention; myocardial infarction; stroke; statin; ACE inhibitor; angiotensin receptor blocker; antiplatelet agent; β-blocker; cardiac rehabilitation

Address for correspondence: Eva Lonn, MD, Professor of Medicine and Cardiology, Hamilton Health Sciences General Site, 237 Barton Street East, Hamilton, Ontario, Canada L8L 2X2, Canada (e-mail: lonnem@mcmaster.ca)
half of the century with rates peaking in the 1950s to 1970s. Unprecedented research efforts both at the basic and clinical level have led to our understanding of many of the underlying pathophysiological mechanisms and epidemiological determinants of CVD and effective therapies have been developed leading to extraordinary progress in reducing mortality and morbidity from CVD in these countries. However, many challenges remain in spite of these advances and new challenges such as increasing rates of obesity and diabetes are emerging, so that CVD remains the major cause of death and disability in most Western countries. By contrast, with the later occurrence of industrialization, urbanization, and economic development and also due to increasing globalization, this epidemiological transition has occurred in the latter half of the twentieth century in many of the developing countries or is expected to occur in the near future in others, with continuing increases expected in most chronic diseases, including CVD, over the next few decades. Thus, CVD, including coronary heart disease (CHD) and its equivalents, is no longer just an affliction of the sedentary Western world, but also of most other regions, so that the epidemic of CVD imposes an ongoing major global health and economic burden. Therefore, it is imperative that health care providers have a comprehensive understanding of available CVD prevention modalities, including primary and secondary prevention strategies.

Increasing insight into vascular biology and the pathogenesis of atherosclerosis has had profound implications in our understanding of CVD and its treatment. The development of pharmacologic agents that intervene on various pathways contributing to atherogenesis offers the potential to have a great impact on halting disease and preventing events. In addition, the evidence for the central role of lifestyle factors as determinants of risk has led to increased efforts toward developing interventions aimed at modifying lifestyle patterns.

Most guidelines including those from Europe and North America recommend intensive secondary prevention in all patients with established CVD, which has been conclusively shown to confer a high risk of subsequent sudden death, myocardial infarction (MI), and stroke. Compelling data derived primarily from randomized controlled trials have shown the benefits of aspirin (or antiplatelets) and angiotensin-converting enzyme (ACE) inhibitors (A), β-blockers and blood pressure–lowering (B), and cholesterol-lowering drugs (C), particularly statins, in preventing recurrent events and improving survival. Taken together, these data are the foundation for the simple, but important advice for secondary prevention—the ABCs. To incorporate lifestyle recommendations into this alphabetic mnemonic, D is for “diet” and “don’t smoke” and E for “exercise.” The ABCDEs have formed the basis for the guidelines for secondary prevention and have the potential to substantially reduce the burden of CVD. Great chal-

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Challenges remain, however, in the implementation of proven pharmacological interventions and in developing efficacious, but also sustainable and widely applicable lifestyle interventions.

This review will summarize current evidence-based approaches to secondary prevention and some of the remaining questions and challenges in the management of patients with known CVD. It needs also to be emphasized that in addition to aggressive preventive strategies in people with preexistent vascular disease, population-based and individualized primary prevention approaches aimed at a wide range of people at risk of developing CVD are essential.

**LESSONS FROM VASCULAR BIOLOGY AND EPIDEMIOLOGY**

Insights into the pathophysiology of atherosclerotic vascular disease have been essential in the development of effective treatment strategies. This review does not attempt to provide a comprehensive overview of the biology of atherosclerotic vascular diseases (excellent reviews on this topic directed at a wide range of clinicians are available). However, a few brief points require special emphasis: (i) atherosclerosis is a complex, progressive disease caused by multiple, complementary pathophysiological mechanisms and therefore the prevention of recurrent events in high-risk people with aggressive disease, which are those targeted in secondary prevention, necessarily requires multiple therapies; (ii) endothelial injury and dysfunction is a critical component of vascular disease, it occurs as a consequence of various CV risk factors and may be modulated by endogenous endothelial repair mechanisms. Improvement in endothelial function should be regarded as a mechanistic target of therapy, although our ability to measure endothelial function remains suboptimal and not yet suited for clinical use; and (iii) fundamental mechanisms involved in the genesis and progression of atherosclerotic lesions and in rendering plaques vulnerable to rupture and consequent catastrophic events include lipid infiltration, oxidation, inflammation, and thrombosis, and should all be targeted by preventive therapies.

Epidemiological data further guide our secondary prevention management. Several important principles merit particular consideration:

- Atherosclerosis is a disease frequently resulting in death and disability and people with preexistent vascular disease are those at highest risk for adverse outcomes. This is best illustrated by older studies conducted prior to the widespread use of effective preventive therapies, which examined the natural history of CVD. Thus, a systematic overview of 23 prospective studies completed prior to 1980 provides data on 14,211 survivors of acute myocardial infarction (MI) and reveals that on average, in the absence of preventive treatment, a patient who “recovered” from MI has a death rate of 10% for the first year following hospital discharge and of 5% per year for each subsequent year for at least 15 years and probably for the rest of his or her life. Considering also, that in the absence of modern therapies, about a third of patients suffering a first acute MI and about half of those with recurrent MI died before reaching the hospital or during hospital admission, these statistics are truly astounding and justify the authors’ conclusion, that effective preventive treatments (including aspirin, statins, β-adrenergic blocking agents, and ACE inhibitors) are essential and should be maintained indefinitely in all survivors of acute MI. More recent statistics suggest that in recent years, in spite of remarkable therapeutic advances, patients with previous MI continue to be at high risk for adverse outcomes, with 18% of men and 35% of women experiencing a recurrent MI, 7% of men and 6% of women sudden death, and 8% of men and 11% of women sustaining a stroke within 6 years after a first MI.

- The major risk factors for CVD in all populations are cholesterol, blood pressure, diabetes (or abnormalities in glucose), tobacco exposure, obesity, insufficient dietary fruits and vegetables, and lack of regular exercise. There is ample evidence that clinicians should not view these risk factors as being “present” or “absent” because the relationship of most risk factors to CVD is continuous and extends over a wide range, including “normal” levels. Moreover, clinical trials of cholesterol and blood pressure lowering suggest that the proportional (or relative) reduction in risk attained depends primarily on the magnitude of cholesterol and blood pressure lowering, irrespective of their starting level. For any proportional reduction in a risk factor level, the absolute benefit derived depends primarily on an individual’s level of risk, and people with previous CV events are at particularly high risk. Therefore, there is value in modifying risk factors in the majority of patients with established CVD, no matter what the level of their risk factors.

- People with diabetes have profound metabolic and vascular alterations and have been shown to be at very high CV risk even in the absence of previous clinical manifestations of atherosclerosis. Therefore, aggressive CV prevention therapies need to be applied to all people with diabetes.
The pathogenesis of acute MI, ischemic stroke, and peripheral arterial disease is attributed to atherosclerosis and thrombosis. Further, the determinants of atherothrombosis in various vascular territories are similar and include all of the conventional risk factors. Interestingly, people with evidence of peripheral arterial disease represent the highest risk subset of all vascular patients and CHD is the major cause of death in this population. Therefore, the need for CV prevention cannot be overlooked in these patients. In spite of their different clinical presentation, the increased risk of future CV events is present in patients irrespective of vascular territory (ie, cerebrovascular, peripheral, or coronary vasculature) in which the clinical manifestation has occurred, and secondary prevention therapies should be applied consistently and aggressively in all vascular patients.

Table I lists categories of patients, who in addition to those with CHD, are at high risk and require secondary CV preventive therapies.

**PHARMACOLOGIC INTERVENTIONS IN SECONDARY CVD PREVENTION**

**Aspirin, antiplatelets, and antithrombotic drugs**

There is strong evidence that antiplatelet agents, in addition to being effective in the setting of acute coronary syndromes and acute stroke (International Stroke Trial [IST]), reduce the risk of recurrent vascular events in people with prior MI, occlusive stroke, transient ischemic attack (TIA), stable angina, coronary artery bypass grafting (CABG) and peripheral arterial disease. The most plausible mechanism for the benefit of aspirin in CVD relates to its ability to permanently inhibit the platelet cyclooxygenase (COX) enzyme (primarily COX-1 in the low doses used in CV prevention), the enzyme required for the production of thromboxane A₂, a powerful promoter of platelet aggregation. More recently, it was suggested that the anti-inflammatory actions of aspirin may contribute to vascular benefits, although the potential for low-dose aspirin to substantially reduce inflammation remains unclear.

The Antithrombotic Trialists’ Collaboration, a comprehensive systematic overview of 195 clinical trials in 135 640 patients at high risk of occlusive arterial disease, reported that 1 month or more of antiplatelet treatment reduced the odds of a vascular event (non-fatal MI, nonfatal stroke, or vascular death) by about one quarter compared with controls (odds reduction 27%; 95% confidence interval [CI], 24%-30%; \( P<0.0001 \)), of nonfatal MI by one third, nonfatal stroke by one quarter, and vascular mortality by one sixth. Absolute reductions in the risk of having a serious vascular event were 36 per 1000 treated for 2 years among patients with previous MI, 38 per 1000 patients treated for 1 month among patients with acute MI, 36 per 1000 treated for 2 years among those with previous stroke or transient ischemic attack, 9 per 1000 treated for 3 weeks among those with acute stroke, and 22 per 1000 treated for 2 years among other high-risk patients, including those with stable angina, peripheral arterial disease, and atrial fibrillation. In each of these high-risk categories, the absolute benefits substantially outweighed the risks of major bleeding. Aspirin was the most widely studied antiplatelet drug, with doses of 75-150 mg daily at least as effective as higher daily doses (500-1500 mg daily), while the effects of doses lower than 75 mg daily were less certain (Figure 1).

More recent trials suggest that thienopyridines such as ticlopidine and clopidogrel may be as good as, or even slightly more effective than aspirin in preventing recurrent vascular events in patients with established CVD. These drugs selectively inhibit ADP-induced platelet aggregation, with no direct effect on the metabolism of arachidonic acid. Aspirin and clopidogrel both inhibit platelet aggregation, but act on different pathways. Therefore, a potentially additive benefit can be envisioned.

The Antithrombotic Trialists’ Collaborative overview reported that, compared with aspirin, clopidogrel reduced the risk of a vascular event by 10% (\( P=0.03 \)). This result is based primarily on the results of the Clopidogrel versus Aspirin in patients at Risk of Ischemic Events (CAPRIE) trial, a large randomized clinical trial of close to 20 000 patients in which a relative risk reduction of MI, stroke, and cardiovascular deaths of 8.7% (\( P=0.043 \)) with clopidogrel 75 mg/day compared with aspirin was observed. Further, more recent evidence suggests that
combination of antiplatelet therapy with a thienopyridine derivative and aspirin in high-risk patients with unstable angina or non–ST-segment elevation MI is more effective than aspirin alone.44 Ongoing trials will help evaluate whether the benefit noted in the Clopidogrel in Unstable Angina to prevent Recurrent Events (CURE) trial up to 1 year following non–ST-segment elevation MI,45 is also observed with chronic long-term therapy of patients with a variety of manifestations of coronary disease.46 In spite of the apparent small advantage of clopidogrel over aspirin in the CAPRIE trial and the potential, but yet to be proven, benefit of adding clopidogrel to aspirin, from a global perspective, considering the very significant economic implications of the widespread long-term use of clopidogrel in a wide range of patients with vascular disease, aspirin remains at least for now the most widely recommended antiplatelet agent in secondary prevention and should be the first-line therapy in the majority of cases.

Antiplatelet therapy is not without risk. Bleeding is the most important adverse effect of antiplatelet treatment. The Antithrombotic Trialists’ Collaboration reported that antiplatelet therapy is associated with an excess risk of intracranial bleeding in trials of long-term treatment. In addition, antiplatelet treatment is associated with a small, but significant excess of nonfatal major extracranial bleeds, but there is no clear excess of fatal extracranial bleeds. Higher-dose antiplatelet therapy appears to be associated with more gastrointestinal bleeding than lower doses.38 The thienopyridines appear to be associated with significantly less gastrointestinal hemorrhage and upper gastrointestinal upset than aspirin. Clopidogrel is safer and better tolerated than ticlopidine. In the CURE trial of more than 12 000 patients with unstable angina or non–ST-segment elevation MI, the combination of clopidogrel and aspirin is associated with a 38% increase in major bleeding, \( P = 0.001 \) (defined as intraocular, or requiring a transfusion of \( \geq 2 \) units), but not life-threatening bleeds (\( P = 0.13 \) (defined as a hemoglobin drop of \( \geq 5 \) g/dL, hypotension needing IV inotropes, surgery to stop bleeding, symptomatic intracranial hemorrhage, or transfusion of \( \geq 4 \) units of blood).44

The role of oral anticoagulant therapy in secondary CV prevention remains less well defined, with risks and obstacles related to the need for monitoring of levels of anticoagulation probably outweighing benefits for most patients. High- and moderate-intensity oral anticoagulation are more effective than control and than aspirin alone, but are associated with an increased risk of major bleeding and the need for very careful INR (international normalized ratio) monitoring.47 Therefore, the routine use of oral anticoagulation post myocardial infarction and in other patients with vascular disease is currently not recommended. Anticoagulant therapy should be considered in patients who do not
tolerate aspirin or other antiplatelet agents and in those with demonstrated left ventricular (LV) mural thrombus, or at high risk for developing mural thrombus and subsequent embolic events, such as patients with recent large anterior MI and major LV wall motion abnormalities.\textsuperscript{5} This indication is strengthened in the presence of atrial fibrillation, congestive heart failure, LV aneurysm, or mural thrombosis detected on echocardiography.\textsuperscript{5} Oral anticoagulants require regular monitoring for intensity of anticoagulant effects and should be used carefully and judiciously due to the excess risk of bleed. Novel oral antithrombotic that do not require the same degree of monitoring as coumarin anticoagulants are under investigation, but not yet available for clinical use.\textsuperscript{48} \\

\textbf{β-Blockers} \\

β-Blockers act by multiple mechanisms to improve outcomes in patients with CHD, especially those with recent acute MI. These include blood pressure lowering, improved balance of oxygen demand and supply, inhibition of sympathetic stimulation of the heart, and decreased ventricular irritability. β-Blockers have proven benefits in the treatment of stable angina, in the post-MI setting, congestive heart failure, and arrhythmias.\textsuperscript{6,51} Several randomized controlled trials found benefits associated with the use of β-blockers post MI and a large systematic overview of over 24 000 people reported that β-blockers improved survival in patients with prior MI by 23%, reduced the risk of sudden death by 30%, and reduced the risk of nonfatal reinfarction by 25%.\textsuperscript{52} While some studies suggested potential differences in the clinical benefits of various β-blockers, later studies and systematic overviews did not identify clear differences between β-blockers with and without cardioselectivity or membrane-stabilizing properties and between those with or without intrinsic sympathomimetic activity. Subgroup analyses demonstrated comparable benefits in men and women and found that β-blockers were particularly effective in subgroups with highest baseline risk such as those over 50 years of age, those with a history of previous MI, hypertension, or early heart failure symptoms post MI.\textsuperscript{53,54} Many of the trials included in these classic meta-analyses are older and precede the common use of other modern therapies. However, more recent studies confirm mortality benefits of β-blockers in the postthrombolytic era and in patients with LV dysfunction post MI.\textsuperscript{55-57} Adverse effects associated with β-blocker use such as bronchospasm, bradycardia, hypotension, heart block, fatigue, depression, nightmares, dizziness, hallucinations, and sexual dysfunction have been reported.\textsuperscript{51,58} However, serious adverse effects are uncommon when...
patients are appropriately selected for therapy. For example, a registry of 54,962 survivors of acute MI over the age of 65 years reported a 15% lower 1-year mortality in patients with chronic obstructive pulmonary disease (COPD) or asthma who were taking a β-blocker, but were not on β-agonist therapy, as compared with those not on β-blocker therapy.59 However, β-blockers conferred no survival benefit to patients who were using a β-agonist or those with severe COPD or asthma. Similarly, although most clinicians are concerned about the use of β-blockers in patients with intermittent claudication, a meta-analysis found no adverse effect of β1-selective blockers on claudication symptoms.60

**SUMMARY AND RECOMMENDATIONS**

β-Blockers are recommended in all patients post MI who can tolerate this therapy.5,51 Treatment should be continued for at least 2 to 3 years and likely indefinitely. Patients with high baseline risk such as those with large infarcts, early heart failure, impaired LV function, hypertension, and ventricular arrhythmias are likely to derive the most benefit. Although relative contraindications may once have been thought to preclude the use of β-blockers in some patients, evidence now suggests that, when administered with appropriate monitoring, the benefits of β-blockers in reducing reinfarction and mortality actually outweigh the risks, even in patients with mild asthma or COPD, insulin-dependent diabetes mellitus, severe peripheral arterial disease, first-degree heart block, and LV dysfunction or heart failure.

**IMPORTANT UNANSWERED QUESTIONS**

β-Blockers do not directly influence the athero-sclerotic process, ie, are not disease-modifying agents. Benefits in very-low-risk post-MI patients, including those with early reperfusion, normal or near-normal LV function, and no ventricular arrhythmias, and in other secondary prevention settings (in patients without previous MI), are less well established.

**Cholesterol lowering with statins and the use of other drugs to treat dyslipidemias**

Epidemiological studies demonstrate a strong and graded association between elevated total and low-density lipoprotein (LDL) cholesterol and CV risk, both in individuals without and those with established CVD.61-67 Low high-density lipoprotein (HDL) cholesterol is also an independent risk factor for atherosclerosis and is associated with poor outcomes in people who already have CVD.63,68,69 Elevated triglyceride concentration also confers an increased vascular risk, although this relationship has been more difficult to establish and remains somewhat controversial.70,71

Lipid-altering agents include several classes of drugs: statins, bile acid sequestrants, nicotinic acid, cholesterol absorption inhibitors, and fibric acid derivatives. Statin drugs are the most effective drugs for lowering LDL cholesterol concentration, with reductions in the range of 20% to 60%, and also lower triglyceride levels by 15% to 35% and raise HDL cholesterol concentration by 5% to 15%.72 Statins are competitive inhibitors of β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting step in cholesterol biosynthesis. The largest and most successful clinical trials of lipid-modifying drugs have used statins. Their beneficial effects are likely not only a consequence of their effect on lipids, but are thought to be mediated by additional pleiotropic actions, the most important being the increase in the bioavailability of nitric oxide (NO).73,74 Thus, statins have been shown to directly upregulate endothelial nitric oxide synthase (eNOS) expression and activity, increasing NO availability, and to improve endothelial function. Statins have also potent anti-inflammatory properties and can favorably alter plaque composition by reducing the accumulation of macrophages and decreasing the expression of extracellular matrix-degrading enzymes, thus favoring plaque stability.75 Animal models of acute inflammation have demonstrated the potent anti-inflammatory properties of statins and clinical trials have shown reductions in C-reactive protein (CRP) and other markers of inflammation in human subjects treated with various statins.76 Other beneficial actions of statins include inhibition of vascular smooth muscle cell proliferation, inhibition of leukocyte adhesion to the endothelium, and enhancement of fibrinolytic pathways.77

A number of large randomized placebo-controlled statin trials conducted in patients with coronary heart disease and diabetes (Table II, next page)78-82 have clearly demonstrated that LDL-cholesterol lowering of about 1.0 mmol/L in people at high risk of ischemic coronary events substantially reduces the risk of major vascular events by about 20%, with reductions in all-cause mortality by about 12%, coronary heart disease and other vascular disease mortality by about 20%, and nonfatal cardiovascular events, including MI.
Clear benefits were shown in all subgroups evaluated, including various age groups, women and men, people with diabetes and those without, and those with cerebrovascular or peripheral arterial disease. The reductions in vascular events were additive to other effective therapies, such as aspirin, β-blockers, and ACE inhibitors. Therefore, statin therapy should be used widely in patients with prior MI and in other vascular disease patients, as well as in people with diabetes and no preexistent clinically manifest vascular disease.

Recent evidence, such as the data provided by the Heart Protection Study, suggests that statin therapy is clearly beneficial even in those vascular disease patients with levels of total cholesterol and LDL cholesterol lower than 5.0 mmol/L and 2.5 mmol/L, respectively. These data support the notion that in patients with coronary heart disease and other high-risk patient sub-sets, there is no clear cutoff value for LDL cholesterol below which there would be no benefit for further lowering it. While most current guidelines recommend LDL-cholesterol lowering to 2.5 mmol/L or lower in post-MI patients, emerging data are challenging these recommendations. A trial conducted in patients treated by prior saphenous vein coronary artery bypass graft surgery found that more aggressive reduction of cholesterol aiming for target LDL cholesterol levels of 1.6-2.2 mmol/L was more effective than a less aggres-
sive treatment regimen in retarding the progression of coronary artery disease. Similar enhanced benefits on retarding the anatomic progression of coronary atherosclerosis were shown for a more aggressive lipid-lowering treatment strategy in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study and large randomized trials such as Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL), Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT), Aggrastat to Zocor (A to Z), and Treating to New Targets (TNT) indicate that early and more aggressive lipid-lowering statin therapy provides more benefit than delayed and less aggressive statin regimens, both in patients with recent acute MI and in those with chronic stable CHD. Based on results of these trials some guidelines have been recently updated and suggest that more aggressive LDL cholesterol lowering (to levels <1.8 mmol/L) should be achieved in secondary prevention.

Other lipid-lowering agents studied in patients with coronary heart disease including those with prior MI include fibrates, omega-3 fatty acids, resins, niacin, and estrogens. The recent Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) reported a 22% reduction in the risk of non-fatal MI and death from coronary causes in middle-aged men with coronary heart disease and “normal” LDL cholesterol concentration treated with gemfibrozil. The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico (GISSI)-Prevenzione trial found benefits associated with omega-3 polyunsaturated fatty acid (PUFA) therapy in patients post MI, although most patients in this trial were not treated with a statin and it therefore remains uncertain if the benefits observed may extend to patients receiving statin therapy. Niacin and resins can be used as adjunctive therapy in addition to statins or in patients who do not tolerate statin therapy and have also been associated with improved outcomes in patients with CHD. Ezetimibe is the first in a new class of cholesterol absorption inhibitors that impair cholesterol absorption at the brush border of the intestine without affecting the absorption of triglycerides or fat-soluble vitamins. It may be particularly helpful in people who cannot tolerate statins in doses required to attain targets of therapy. For example, a randomized trial found that the reduction in LDL concentration was the same with atorvastatin 10 mg/day and ezetimibe 10 mg/day, as with atorvastatin 40 mg/day and simvastatin 80 mg/day. The ABC of secondary cardiovascular prevention - Lonn and Grewal

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<td>Any major coronary event</td>
<td>3337 (7.4)</td>
<td>4420 (9.8)</td>
<td></td>
<td>23% (20%, 26%)</td>
</tr>
<tr>
<td>CABG</td>
<td>713 (3.3)</td>
<td>1006 (4.7)</td>
<td></td>
<td>25% (18%, 31%)</td>
</tr>
<tr>
<td>PTCA</td>
<td>510 (2.4)</td>
<td>658 (3.1)</td>
<td></td>
<td>21% (11%, 31%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1397 (3.1)</td>
<td>1770 (3.9)</td>
<td></td>
<td>24% (16%, 31%)</td>
</tr>
<tr>
<td>Any coronary revascularization</td>
<td>2620 (5.8)</td>
<td>3434 (7.6)</td>
<td></td>
<td>24% (20%, 27%)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>105 (0.2)</td>
<td>99 (0.2)</td>
<td></td>
<td>-5% (-41%, 22%)</td>
</tr>
<tr>
<td>Presumed ischemic stroke</td>
<td>1235 (2.8)</td>
<td>1518 (3.4)</td>
<td></td>
<td>19% (11%, 26%)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1340 (3.0)</td>
<td>1617 (3.7)</td>
<td></td>
<td>17% (12%, 22%)</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>6354 (14.1)</td>
<td>7994 (17.8)</td>
<td></td>
<td>21% (19%, 23%)</td>
</tr>
<tr>
<td>Any death</td>
<td>3832 (8.5)</td>
<td>4354 (9.7)</td>
<td></td>
<td>12% (9%-16%)</td>
</tr>
</tbody>
</table>

Statin treatment is generally well tolerated and have few side effects. Large randomized trials have not substantiated earlier concerns about increased cancer risk and hazards related to accidental and violent death. Clinical trials and postmarketing surveillance data demonstrate that all currently available statins are generally well tolerated and that serious adverse effects, such as rhabdomyolysis (<0.01%) and hepatitis (<0.01%) are exceedingly rare (even when using high-dose regimens). Other lipid-lowering agents studied in patients with coronary heart disease including those with prior MI include fibrates, omega-3 fatty acids, resins, niacin, and estrogens. The recent Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) reported a 22% reduction in the risk of non-fatal MI and death from coronary causes in middle-aged men with coronary heart disease and “normal” LDL cholesterol concentration treated with gemfibrozil. The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico (GISSI)-Prevenzione trial found benefits associated with omega-3 polyunsaturated fatty acid (PUFA) therapy in patients post MI, although most patients in this trial were not treated with a statin and it therefore remains uncertain if the benefits observed may extend to patients receiving statin therapy. Niacin and resins can be used as adjunctive therapy in addition to statins or in patients who do not tolerate statin therapy and have also been associated with improved outcomes in patients with CHD. Ezetimibe is the first in a new class of cholesterol absorption inhibitors that impair cholesterol absorption at the brush border of the intestine without affecting the absorption of triglycerides or fat-soluble vitamins. It may be particularly helpful in people who cannot tolerate statins in doses required to attain targets of therapy. For example, a randomized trial found that the reduction in LDL concentration was the same with atorvastatin 10 mg/day and ezetimibe 10 mg/day, as with atorvastatin 40 mg/day and simvastatin 80 mg/day. The ABC of secondary cardiovascular prevention - Lonn and Grewal


Abbreviations: CABG, coronary artery bypass grafting; CHD, coronary heart disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.
tatin 80 mg alone. However, to date, no clinical outcome trials have demonstrated benefits with ezetimibe. Such trials are ongoing and will better define the role of this lipid-modifying agent in secondary prevention. New agents, such as cholesterol ester transfer protein inhibitors and other agents that mobilize reverse cholesterol transport from vascular cells are currently undergoing clinical trials and may further improve our management of high-risk patients.

Angiotensin-converting enzyme (ACE) inhibitors and other drugs that modulate the renin-angiotensin-aldosterone system (RAAS)

The renin-angiotensin-aldosterone system (RAAS) is critically involved in the pathogenesis of vascular disease and is an important therapeutic target. The RAAS releases angiotensin II, a potent vasoconstrictor, which raises blood pressure and promotes atherosclerosis by increasing oxidative stress, inflammation, endothelial dysfunction, vascular growth, and by inhibiting endogenous fibrinolysis. The RAAS interacts with the kallikrein-kinin system, which releases bradykinin. The effects of bradykinin in the vasculature oppose many of the actions of angiotensin II; it stimulates synthesis of vasodilators, such as NO, hyperpolarizing factor, and prostacyclin, which improve endothelial function; it inhibits platelet adhesion and smooth muscle cell proliferation and enhances the fibrinolytic balance by stimulating tissue plasminogen activator (t-PA) synthesis. ACE inhibitors act by dual pathways to prevent angiotensin II formation and to block the degradation of bradykinin into inactive peptides. By decreasing angiotensin II and increasing bradykinin, ACE inhibitors exert multiple effects that protect the coronary and peripheral vasculature.

Earlier clinical trials have clearly demonstrated the benefits of ACE inhibitors in hypertension, heart failure, asymptomatic LV dysfunction, and in patients with recent MI and low LV ejection fraction. More recent trials have evaluated the effects of ACE inhibitors in patients with CHD or arterial disease in other vascular territories in the absence of heart failure and with preserved (normal or near-normal) LV systolic function. Surrogate end point trials have shown dose-dependent improvement in LV structure and function, endothelial function, and in slowing the atherosclerotic process. Large clinical end point trials confirm general reductions in morbidity and mortality, although there are differences in the design and results of these trials. The Heart Outcomes Prevention Evaluation (HOPE) study, demonstrated that 4 to 6 years of treatment with 10 mg daily of ramipril reduced major vascular events, deaths, and new diabetes in patients with preserved ventricular function and vascular disease or high-risk diabetes. The benefits of ACE inhibitors were also confirmed by the EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA), where-
as the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial reported no reduction in CV in patients with stable coronary artery disease treated with trandolapril. Some have interpreted the PEACE trial results as evidence for lack of benefit from ACE-inhibitor therapy in "low-risk" patients with CHD, or those who are receiving other effective therapies (especially statins and revascularization). However, careful review of the totality of data provided from these three large trials shows that ACE-inhibitor therapy does indeed reduce all-cause death by about 14% and major vascular events by about 19% in a wide range of patients with vascular disease and preserved LV systolic function, including those receiving other cardiac and vascular protective therapies (statins, aspirin, β-blockers), people of various ages including the elderly, men, and women, and those with or without a history of hypertension, diabetes, and peripheral arterial disease. Based upon these findings, the 2004 task force of the European Society of Cardiology (ESC) gave a class I recommendation to the use of ACE inhibitors in patients with vascular disease.

Patients with type 2 diabetes are particularly suited for ACE-inhibitor therapy, with substantial reductions in macrovascular events, CV death, MI, and stroke, and in microvascular disease, particularly nephropathy, as shown in the Microalbuminuria, Cardiovascular and Renal Outcomes–Heart Outcomes Prevention Evaluation (MICRO-H totalPrice) trial. However, differences in the ACE inhibitors used and the play of chance cannot be fully excluded.
tion (MICRO-HOPE) substudy of HOPE 120 and the PERindopril SUbstudy in coronary Artery disease and DiabEtes (PERSUADE) trial,121 a substudy of EUROPA, as well as in other studies. A particularly interesting and somewhat unexpected finding is the reduction in new diagnoses of diabetes in patients treated with ACE inhibitors,122 which was observed in retrospect in several trials and which is further explored in ongoing studies.123

ACE inhibitors are generally well tolerated. The most common side effects include cough, occurring in 5% to 10% of patients. Dizziness, hypotension, renal dysfunction, and hyperkalemia are infrequent and can generally be avoided by careful drug titration and by avoiding the administration of ACE inhibitors in volume-depleted patients and in those with bilateral renal artery stenosis.

Angiotensin-receptor blockers (ARBs) irreversibly inhibit angiotensin II binding to the angiotensin receptor subtype 1 (AT1), thought to account for most deleterious actions of RAAS. The effect on AT1-mediated effects of angiotensin II is more profound than that attained with ACE inhibitors, because angiotensin II can be produced via alternate non-ACE-mediated pathways. However, ARBs do not directly affect bradykinin breakdown (the interaction with the kallikrein-kinin system via AT2 receptor activation is less well understood and probably less important), and the results of increased availability of angiotensin II associated with AT1 blockade remain uncertain. To date, ARBs have been shown to: (i) effectively lower blood pressure with excellent tolerability in hypertensive patients124; (ii) reduce hospital admissions in patients with chronic heart failure125; (iii) represent a viable option for the treatment of patients with acute MI and significant LV systolic dysfunction126, and (iv) to halt the progression of renal disease in patients with type 2 diabetes mellitus.127-129 Similar to ACE inhibitors, these agents seem to prevent or delay the onset of type 2 diabetes and are under investigation for this potentially important clinical application. Benefits of ARBs alone or in combination with ACE inhibitors in the treatment of a wide range of patients with coronary and other vascular disease have been suggested, but remain still unproven. The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND)
study in over 30,000 patients with preexistent CV disease, but without heart failure or LV dysfunction, is expected to provide further answers. For now, it seems reasonable to use ARBs in ACE-intolerant patients, although this approach remains unproven. Aldosterone blockade with drugs such as spironolactone and eplerenone has been shown to benefit patients with hypertension, advanced heart failure, and those with LV dysfunction post MI, but has not been tested in other settings.

**SUMMARY AND RECOMMENDATIONS**

ACE inhibitors are recommended in all patients post MI who can tolerate this therapy. Treatment should be initiated in the early phases of acute MI and continued indefinitely post MI. Other patients with vascular disease, including those with previous stroke and TIA, peripheral arterial disease, and type 2 diabetes with additional risk factors should also receive ACE-inhibitor therapy. ARBs can be used in heart failure patients already receiving an ACE inhibitor, in patients with type 2 diabetes with nephropathy, and may be considered in other high-risk people who do not tolerate ACE inhibitors.

**IMPORTANT UNANSWERED QUESTIONS**

It remains uncertain whether all ACE inhibitors should be used in patients with stable coronary and other vascular disease in the absence of heart failure. The ACE-inhibitor preparations proven to reduce events are the high-tissue affinity, lipophilic agents, specifically ramipril 10 mg/day and perindopril 8 mg/day. The role of ARBs in the absence of heart failure and diabetic nephropathy requires further exploration.

**Drugs and supplements with no proven benefit and potential for harm**

Several drugs and supplements have been commonly used in secondary prevention. However, recent evidence does not support the use of certain agents including (i) vitamin E and other antioxidant vitamins; (ii) hormone replacement therapy (HRT) in postmenopausal women; and (iii) Class I antiarrhythmic agents (quinidine, procainamide, disopyramide, encainide, flecainide, moricizine).

Oxidation was shown conclusively to play a major role in atherogenesis and large prospective epidemiological studies suggested that the use of antioxidant vitamins, particularly vitamin E supplements, may be protective. However, a considerable number of large randomized clinical trials have failed to confirm benefit. Antioxidant vitamins were shown to have a neutral effect in most settings, with a potential for harm in some patients, such as those at risk of developing heart failure and when using high-dose preparations. Importantly, the use of antioxidant vitamins and that of other “natural” products often detracts from the focus and commitment needed to implement interventions proven to reduce risk. It should be noted that homocysteine-lowering B vitamins (folate and vitamins B6 and B12) are still under investigation in large clinical trials.

The use of estrogen, alone or in combination with progesterone, did also hold promise, based on findings derived from over 50 observational studies and from investigations indicating that HRT has favorable effects on lipids, endothelial function, and arterial vasodilation. Unfortunately, clinical trials do not substantiate the use of HRT in CV prevention. In fact, the Women’s Angiographic Vitamin and Estrogen (WAVE) trial found that angiographic progression of coronary disease worsened in women receiving HRT and the Heart and Estrogen/progestin Replacement Study (HERS) trial in 2763 women with CHD reported no differences in CV outcomes between women randomized to 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone or placebo and an excess of venous thromboembolic events in those allocated to HRT. Similar disappointing results were shown in primary prevention trials. Therefore, given current information, HRT should not be used to reduce the risk of CV events in postmenopausal women.

The data for Class I antiarrhythmic agents clearly indicate a substantial hazard related primarily to the proarrhythmogenic potential of these agents in patients with structural heart disease.
CARDIAC REHABILITATION AND LIFESTYLE MODIFICATIONS

Comprehensive cardiac rehabilitation programs include medical evaluation, education, counseling, prescribed exercise, and CV risk factor modification, directed towards smoking cessation, the recognition and management of psychosocial stressors, weight management, treatment of dyslipidemia, hypertension, and diabetes, and using pharmacological, as well as non-pharmacological approaches. Goals of therapy in patients with established CV disease are outlined in Table V. Such comprehensive intensive approaches can achieve substantial success, as shown in people with type 2 diabetes, where aggressive comprehensive management of risk factors was shown to reduce CV events by over 50% compared with usual care. Comprehensive cardiac rehabilitation programs were shown to reduce the risk of cardiovascular deaths by 20% to 25% and reduce cardiac morbidity.

It needs to be strongly emphasized that lifestyle modifications are essential components of the management of patients with coronary heart disease and need to be an integral component of secondary prevention strategies. This publication does not aim to review in detail the evidence supporting the implementation of lifestyle modifications. Such evidence is available for smoking cessation, dietary modifications, regular exercise, and psychological and stress management, and is reviewed in brief.

Smoking cessation

Many observational studies found that people with CHD who stopped smoking rapidly reduced the risk of cardiac disease and MI (relative risk reduction about 50% for recurrent coronary events or premature death compared with continuing smokers). About half of the benefits occur in the first year after smoking cessation, followed by a more gradual decrease in risk reaching the risk of never smokers after several years of abstinence. Among people with peripheral arterial disease and stroke, smoking cessation has been shown in observational studies to be associated with improved exercise tolerance, decreased risk of amputation, improved survival, and reduced risk of recurrent stroke. The interventions shown to be most effective to attain and sustain smoking cessation are referral to a smoking cessation program and the use of nicotine patches or gum and bupropion.

Dietary modifications and management of weight and increased abdominal adiposity

Dietary intervention, such as a Mediterranean diet, rich in fish (particularly oily fish), fruit, vegetables, bread, pasta, potatoes, olive oil and rapeseed margarine can be highly effective in patients with established CHD. Other diets shown to be beneficial are low-fat and high-fiber diets. Dietary recommendations need to emphasize the need to limit energy intake adjusted to maintain ideal body weight, intake of

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Goal of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular disease</td>
<td>Aspirin, β-blocker, statin, and ACE-inhibitor in all patients who can tolerate these therapies independent of levels of risk factors</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>$&lt; 130/80$ mm Hg</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>$\text{HgA}_1\text{C} &lt; 7%$</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>$&lt; 2.5$ mmol/L ($&lt; 1.8$ mmol/L should be strongly considered)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>$&gt; 1.1$ mmol/L in men</td>
</tr>
<tr>
<td></td>
<td>$&gt; 1.3$ mmol/L in women</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>$&lt; 1.7$ mmol/L</td>
</tr>
<tr>
<td>Excessive body weight</td>
<td>Body mass index (BMI) $&lt; 25$ kg/m$^2$</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>30-45 minutes of moderate intensity exercise at least 5 days/week</td>
</tr>
</tbody>
</table>

Table V. Treatment goals in the secondary prevention of cardiovascular events.
saturated fats, not to exceed 30% of total lipids, of cholesterol (<300 mg/day) and of complex carbohydrates, as well as the need to ensure adequate intake of micronutrients.

**Regular exercise**

Exercise is an important component of cardiac rehabilitation programs that has been demonstrated to reduce by 20% to 25% the risk of cardiovascular death in patients with previous MI. Current recommendations suggest 30 to 45 minutes of moderate physical activity at least 5 days a week.

**Psychological and stress management interventions**

Depression and other forms of psychological stress were shown to be associated with increased CV risk. A systematic overview in over 3000 people with CHD found that psychosocial treatments significantly reduced mortality and nonfatal events in the first 2 years of follow-up after MI (relative risk reduction of about 40% for different CV end points).

**CHALLENGES AHEAD**

Our biggest current challenge is to implement proven effective therapies in all high-risk patients with CVD. A clear gap between physician knowledge of treatment benefits and clinical reality has been noted and needs to be narrowed. For example, the Second EUROpean Action on Secondary Prevention by Intervention to Reduce Events (EUROASPIRE II) survey, conducted in nine European countries in 1999/2000, 5 years after the EUROASPIRE I survey of 1995/1996, found little change in smoking and hypertension rates among people with CHD, alarming increases in rates of obesity and diabetes, while blood pressure control was achieved only in about half of the patients assessed and many were not receiving life-saving medications. Similar data are available from the USA, Canada, and other regions. Initiatives directed at the systematic implementation of secondary prevention interventions are gaining increasing popularity and novel approaches such as the “polypill” have been proposed. In addition, more physician and patient education, as well as research into barriers in the implementation of CV prevention, are needed.

### CONCLUSIONS

The potential gains associated with the consistent use of pharmacological secondary prevention interventions are very large. Aspirin, β-blockers, ACE inhibitors, and lipid-lowering therapies lower the risk of future vascular events by about 25% each in high-risk patients. The benefits of these interventions appear to be largely independent, so that when used together it is expected that two thirds to three quarters of future vascular events could be prevented. When in addition to these drug therapies smoking cessation and aggressive blood-pressure lowering are attained, it may be possible to lower the risk of future vascular events by about four fifths in high-risk people.

**Table VI.** Potential cumulative impact of treatment with drugs proven to improve outcomes in the secondary prevention of coronary heart disease in other high-risk patients.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative risk reduction*</th>
<th>2-Year event rate†</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>…</td>
<td>8%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>25%</td>
<td>6%</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>25%</td>
<td>4-5%</td>
</tr>
<tr>
<td>Lipid-lowering (by 1.5 mmol/L)</td>
<td>30%</td>
<td>3.0%</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>25%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

*Cumulative risk reduction if all drugs are used is about 75%.
†“Events” designates cardiovascular death, myocardial infarction, or strokes. A 4% annual event rate is assumed in the absence of secondary prevention therapies. Smoking cessation in current smokers, dietary modifications, regular exercise, and psychosocial counseling are likely to lead to substantial additional benefits.

Given these tremendous potential gains, making these interventions available, affordable, accessible, and convenient, as well as understanding current barriers to the implementation of secondary CV prevention interventions, both in established market economies and in developing countries, needs to be a priority and could lead to substantial individual and public health benefits.
REFERENCES

1. Yusuf S, Ounpuu S.
Tackling the growing global burden of atherosclerotic cardiovascular diseases.

Global burden of cardiovascular diseases. Part I: general considerations, the epidemiological transition, risk factors, and impact of urbanization.


European guidelines on cardiovascular disease prevention in clinical practice.

ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction),

ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina).

Evidence-based guidelines for cardiovascular disease prevention in women.


American College of Cardiology Chronic Stable Angina Panel. Primary care management of chronic stable angina and asymptomatic suspected or known coronary artery disease: a clinical practice guideline from the American College of Physicians.

10. Cohen JD.
ABCs of secondary prevention of CHD: easier said than done.

11. Ross R, Glomset JA.
The pathogenesis of atherosclerosis (first of two parts).

12. Ross R, Glomset JA.
The pathogenesis of atherosclerosis (second of two parts).


14. Fuster V, Morena PR, Fayard ZA, Corti R, Badimon JJ.
Atherosclerosis and high-risk plaque: part I: evolving concepts.

15. Ross R.
Atherosclerosis: an inflammatory disease.

16. Libby P.
Inflammation and atherosclerosis.

17. Libby P, Ridker PM.
Inflammation and atherosclerosis.

New markers of inflammation and endothelial cell activation: Part I.

Biomarkers of vascular disease linking inflammation to endothelial activation: Part II.
20. Griendling KK, Garret FA. 

Role of oxidative stress in atherosclerosis. 
Am J Cardiol. 2003;91:7A-11A.

22. Behrendt D, Ganz P. 
Endothelial function: from vascular biology to clinical applications. 
Am J Cardiol. 2002;90(suppl):40L-48L.

23. Verma S, Anderson TJ. 
Fundamentals of endothelial function for the clinical cardiologist. 

24. Lerman A, Zeiher AM. 
Endothelial function: cardiac events. 

25. Law MR, Wald NJ. 
Risk factor thresholds: their existence under scrutiny. 
BMJ. 2002;324:71-86.

26. Law MR, Wald NJ, Morris JK, Jordan RE. 
Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. 
BMJ. 2003;326:1427.

27. Law MR, Wald NJ, Morris JK, Jordan RE. 
Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. 
BMJ. 2003;326:1427.

28. Law MR, Wald NJ. 
The underlying risk of death after myocardial infarction in the absence of treatment. 

29. Yusuf S, Hawken S, Ounpuu S. 
Effect of potentially-modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. 

30. Law MR, Wald NJ. 
Risk factor thresholds: their existence under scrutiny. 
BMJ. 2002;324:1570-1576.

31. Law MR, Wald NJ, Rudnitska AR. 
Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. 
BMJ. 2003;326:1423.

32. Patrano C, Bachman F, Baigent C, et al, for the Task Force on the Use of Antiplatelet Agents in Patients with Cardiovascular Disease of the European Society of Cardiology. 
Expert consensus document on the use of antiplatelet agents. 

33. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. 
Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. 

34. Criqui MH, Denenberg JO. 
The generalized nature of atherosclerosis: how peripheral arterial disease may predict adverse events from coronary artery disease. 

The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute ischaemic stroke. 

Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. 

37. Antithrombotic Trialists' Collaboration. 
Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. 
BMJ. 2002;324:71-86.

38. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. 
Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. 
41. CAPRIE Steering Committee.  
A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE).  

42. Hass WK, Easton JD, Adams HP, et al.  

43. Hankey GJ, Sudlow CL, Dunbabin DW.  
Thienopyridines or aspirin to prevent stroke and other serious vascular events in patients at high risk of vascular disease? A systematic review of the evidence from randomized trials.  

44. Yusuf S, Zhao F, Mehta SR, Tognoni G, Fox KK.  
Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation.  

45. Sabatine MS, Cannon CP, Gibson CM, et al.  
Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation.  

Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial.  

47. Anand SS, Yusuf S.  
Oral anticoagulants in patients with coronary artery disease.  

48. Weitz JI, Hirsch J, Samama MM.  
New anticoagulant drugs: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.  
Chest. 2004;126(suppl):265S-296S.

49. Campbell CL, Steinshubl SR.  
Variability in response to aspirin: do we understand the clinical relevance?  

Platelet Physiology Subcommittee of the Scientific and Standardization Committee of International Society of Thrombosis and Hemostasis Working Group on Aspirin Resistance: Position paper of the working group on an aspirin resistance.  

51. The Task Force on Beta-Blockers of the European Society of Cardiology.  
Expert consensus document on beta-blockers.  

Beta blockade during and after myocardial infarction: an overview of the randomized trials.  

The beta-blocker pooling project (BBPP): subgroup findings from randomized trials in post infarction patients.  

54. Gottlieb SS, McCarter RJ, Vogel RA.  
Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction.  

Beta blockade after myocardial infarction: systematic review and meta regression analysis.  

56. Nuttall SL, Toescu V, Kendall MJ.  
Beta blockade after myocardial infarction. Beta blockers have key role in reducing morbidity and mortality after infarction.  

57. Dargie HJ.  
Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial.  

58. Ko DT, Hebert PR, Coffey CS, et al.  
Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction.  
JAMA. 2002;288:351-357.

Effectiveness of beta-blocker therapy after acute myocardial infarction in elderly patients with chronic obstructive pulmonary disease or asthma.  

60. Radack K, Deck C.  
Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials.  
61. Law MR, Wald NJ, Thompson SG.  
By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease?  

Serum cholesterol level and mortality findings for men screened in the Multiple Risk factor Intervention Trial Research Group.  

Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S).  
**Circulation.** 1998;97:1452-1460.

64. Simes RJ, Marschner IC, Hunt D, et al.  
Relationship between lipid levels and clinical outcomes in the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels.  
**Circulation.** 2002;105:1162-1169.

Underestimation of the importance of blood pressure and cholesterol for coronary heart disease mortality in old age.  
**Eur Heart J.** 2002;23:286-293.

Serum cholesterol and long-term prognosis in middle-aged men with myocardial infarction and angina pectoris. A 16-year follow-up of the Primary Prevention Study in Göteborg, Sweden.  
**Eur Heart J.** 1997;381:754-761.


68. Abbott RD, Wilson PW, Kannel WB, Castelli WP.  
High density lipoprotein cholesterol, total cholesterol screening and myocardial infarction. The Framingham Study.  
**Atherosclerosis.** 1988;8:207-211.

The Munster Heart Study (PROCAM). Results of follow-up at 8 years.  

70. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F.  
High triglycerides and low HDL cholesterol and blood pressure and risk of ischemic heart disease.  

71. Ginsberg HN.  
**Ann Intern Med.** 1997;126:912-914.

Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study).  
**Am J Cardiol.** 1998;81:582-587.

73. Williams JK, Sukhova GK, Harrington DM, Libby P.  
Pravastatin has cholesterol-lowering independent effects on the artery wall of atherosclerotic monkeys.  
**J Am Coll Cardiol.** 1998;31:684-691.

74. Martinez-Gonzalez J, Raposo B, Rodriguez C.  
3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition prevents endothelial NO synthase downregulation by atherogenic levels of native LDLs.  

Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization.  
**Circulation.** 2001;103:926-933.

76. Albert MA, Danielson E, Rifai N, Ridker PM; PINCE Investigators.  
Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study.  
**JAMA.** 2001;286:64-70.

Simvastatin has anti-inflammatory and anti-atherosclerotic activities independent of plasma cholesterol lowering.  

Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S).  
**Lancet.** 1994;344:1383-1389.

The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels.  

80. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group.  
The Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels.  


121. Daly CA, Fox KM, Remme ME, Ferrari R, Simoons ML.
The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: results from the PERSUADE substudy.

Ramipril and the development of diabetes.

123. Gerstein HC, Yusuf S, Holman R, Bosch J, Pogue J; the DREAM Trial Investigators.
Rationale, design and recruitment characteristics of a large, simple international trial of diabetes prevention: the DREAM trial.

Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE); a randomised trial against atenolol.

Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme.

Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both.


Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes.

Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy.

Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE In tolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials.

The effect of spironolactone on morbidity and mortality in patients with severe heart failure.

132. Brown NJ.
Eplerenone: cardiovascular protection.

Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction.

134. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum J.
Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity.

135. Jha P, Flather M, Lonn E, Farkouh M, Yusuf S.
The antioxidant vitamins (E, C and beta-carotene) and cardiovascular disease: a critical summary of epidemiological and clinical trial data.

136. Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ.
Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials.

Effects of long-term vitamin E supplementation on cardiovascular events and cancer. The HOPE study extension.

Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality.


159. LaBresh KA, Ellrodt AG, Gliklich R, Liljestrand J, Peto R.
Get with the guidelines for cardiovascular secondary prevention: pilot results.

160. Wald NJ, Law R.
A strategy to reduce cardiovascular disease by more than 80%.

161. Yusuf S.
Two decades of progress in preventing vascular disease.

What is the best way to keep the renin-angiotensin system under control?

Alistair S. Hall, MB, ChB, FRCP, PhD; Niamh Kilcullen, MB, BCh, MRCPI

Professor of Clinical Cardiology (A. S. Hall) and BHF Research Fellow (N. Kilcullen)

BHF Heart Research Centre at Leeds - UK

Powerful evidence supports the long-term prescription of angiotensin-converting enzyme (ACE) inhibitors in patients surviving an acute myocardial infarction (AMI) to enhance morbidity and survival outcomes. Nevertheless, while physicians are prescribing ACE-inhibitor therapy to many patients at high-risk of death, there continues to be a failure to prescribe appropriate ACE-inhibition regimens, resulting in an increase in subsequent patient death. Alternate use of an angiotensin receptor blocker (ARB) may be considered—though members of this class are also not readily interchangeable with each other or with the ACE inhibitors. The selective aldosterone antagonist eplerenone may represent a better alternative than do the ARBs for ACE-intolerant patients, though whatever the strategy, there is still the need to ensure that appropriate treatment dose and frequency are used.

Selected abbreviations and acronyms:

- AIRE: Acute Infarction Ramipril Efficacy
- AMI: acute myocardial infarction
- ARB: angiotensin receptor blocker
- ELITE-2: Evaluation of Losartan In The Elderly–2
- EMMACE: Evaluation of Methods and Management of Acute Coronary Events
- EPHELUS: Eplerenone Post-acute myocardial infarction Heart failure Efficacy and Survival Study
- EUROPA: European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease
- GISSI: Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico
- HOPE: Heart Outcomes Prevention Evaluation
- HR: hazard ratio
- ISIS: Internatinal Study of Infarct Survival
- MI: myocardial infarction
- OPTIMAAAL: OPtimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan
- PEACE: Prevention of Events with Angiotensin Converting Enzyme
- RCT: randomized controlled trial
- SAVE: Survival And Ventricular Enlargement
- TRACE: TRAndolapril Cardiac Evaluation
- VALIANT: VALsartan In Acute myocardial InfarctIon
tion. However, the definition of myocardial infarction has broadened over the last few years and now encompasses patients previously considered to have a diagnosis of unstable angina. This has left a gap in the evidence base that is best addressed by broadening the definition of “secondary prevention” to include all patients with overt coronary artery disease, whether stable or unstable. In this setting, three large placebo-controlled studies have been completed. Together with information obtained from acute coronary syndrome registries and also applied clinical common sense, this forms the basis for consideration of the question—“Secondary prevention: what is the best way to keep the renin-angiotensin system under control?”

**DIRECT RCT EVIDENCE FOR ACE INHIBITION?**

Four randomized controlled trials (RCTs) elected to treat individuals with suspected AMI starting within the first 36 hours after the onset of symptoms, of which two reported no beneficial effect on survival. In contrast, both the International Study of Infarct Survival–4 (ISIS-4) and Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico–3 (GISSI-3) trials observed a small survival benefit at 35 to 42 days, which was no longer statistically significant on long-term follow-up. In contrast, the Survival And Ventricular Enlargement (SAVE) and TRAndolapril Cardiac Evaluation (TRACE) investigators randomized individuals with confirmed AMI and evidence of systolic left ventricular (LV) impairment; both studies observed a sustained survival benefit with continued ACE-inhibitor therapy. Similarly, treatment of patients with clinical LV failure after AMI resulted in major and sustained survival benefits as demonstrated by the Acute Infarction Ramipril Efficacy (AIRE) and AIRE Extension (AIREX) studies.

Expert statements and guidelines published in 1996 and 1997 summarized and interpreted evidence available at that time in differing ways. However, despite alternate interpretation as to the value of ACE-inhibitor therapy in secondary prevention, there was agreement that individuals with either clinical LV failure or systolic LV impairment should be treated indefinitely. Furthermore, the recommendation that trial treatment regimens be followed whenever possible was widely endorsed. Importantly, potential differences in the magnitude of survival benefits resulting from different ACE-inhibitor regimens have been inadequately explored.

**DIRECT RCT EVIDENCE FOR ANGIOTENSIN RECEPTOR BLOCKADE**

The OPtimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) and VALsartan In Acute myocardial infarction (VALIANT) studies have compared angiotensin receptor blockers (ARBs), losartan, and valsartan against the first-genera- tion, sulfhydryl-containing ACE inhibitor captopril. The choice of this particular drug as comparator (also used in many comparative heart failure and hypertension trials) is an interesting one given captopril’s limitations as an ACE inhibitor.

Modeled on the terminal proline amino acid of a peptide derived from the venom of the Brazilian viper Bothrops jararaca, captopril utilized a sulfhydryl active moiety to produce ACE inhibition. As this drug was initially associated with a range of unacceptable side effects such as proteinuria, skin rashes, altered taste, other pharmaceutical companies opted to replace the sulfhydryl group with a carboxyl moiety. The potency of the interactions with the active site of the ACE of the carboxyl group was seen to relate to the degree of lipophilicity of the molecule—a property that would later prove to be an asset with regard to both: (i) access to a later discovered second active site on ACE molecule, and (ii) penetration of the ACE inhibitor into normal and pathological tissues.

The OPTIMAAL study compared losartan 50 mg once daily with captopril 50 mg three times daily, in 5477 patients with confirmed AMI and acute heart failure OR anterior Q waves OR prior to MI. The all-cause mortality at a mean follow-up time of 2.7 years was higher for the losartan group (18%) than for the captopril group (16%) producing an increased relative risk of 13% (95% confidence interval [CI], –1% to 28%, P=0.07) and an increased absolute risk of 2% (20 extra deaths per 1000 treated, number needed to harm [NNH] = 50). The secondary end point of cardiovascular death was also increased (hazard ratio [HR], 1.17; 95% CI, 1.01 to 1.34, P=0.034). The authors concluded that ACE inhibitors should remain first-choice therapy.

As the Evaluation of Losartan In The Elderly–2 (ELITE-2) heart failure study also showed a strong trend toward increased mortality with losartan as compared with captopril, the FDA decided to withdraw the drug’s heart failure license. Reasons for lack of efficacy have been debated—predominantly to suggest that an inadequate dose was tested. However, as a produg dependent on first-pass metabolism in the liver, losartan is converted into two different metabolites. The first of these (EXP3174) is a potent
the combination of “A + B,” the mortality outcomes would have been identical to each other as in this trial. Consequently, the conclusions of this study depend heavily on the belief that captopril 150 mg daily is as effective an ACE-inhibitor regimen as are the alternatives. As there have been no conventional heart failure studies performed with captopril, the premise of efficacy is based entirely on the SAVE Study.

It is interesting to note that the 2-year placebo group mortality in SAVE was approximately 17% (ie, identical to VALIANT). However, comparisons are made difficult by: (i) the use of other concomitant medicines; (ii) differing time from MI to randomization; and (iii) percentage of patients with Killip Class >II. These and other differences between the two studies serve to emphasize the inappropriateness of extrapolating a survival benefit from SAVE to VALIANT.

**DIRECT RCT EVIDENCE FOR ALDOSTERONE ANTAGONISM**

The Eplerenone Post-acute myocardial infarction Heart failure Efficacy and Súrvival Study (EPHESUS) evaluated the aldosterone antagonist eplerenone in 6632 patients with heart failure or asymptomatic LV dysfunction after MI and was reported in 2005. Patients with an average age of 64 y were randomized to placebo or eplerenone 50 mg/day and treated for a mean of 16 months. At that time there was a 15% relative risk reduction (95% CI 4% to 25%, P=0.008). These benefits were in the presence of concomitant treatment with ACE inhibitors/ARBs (86%, drugs and dosages not stated) and also β-blockers (75%). Baseline use of statin therapy was surprisingly low (47%). These benefits were in spite of the fact that serious hyperkalemia (>6 mmol/L) occurred in 5.5% of patients given eplerenone as compared with 3.9% given placebo (P=0.002). Conversely, hypokalemia was lower for eplerenone.

These findings are supported by earlier observations for heart failure patients given spironolactone as part of the Randomized ALdactone Evaluation Study (RALES). Hence the repeated question of whether a “class effect” is being observed. In essence, concern has been raised that the newer more selective aldosterone antagonist eplerenone may be no better than the less selective, though much cheaper, drug spironolactone.

Importantly, neither drug has demonstrated the ability to prevent myocardial infarction—a common cause of death in these patients. Consequently, this is unlikely to be the “best way to modulate the renin-angiotensin system” for the majority of patients in need of secondary prevention.

**EXTENDED RCT EVIDENCE FOR ACE INHIBITION**

The HOPE study recruited 9297 high-risk men and women, >55 years of age, with previous cardiovascular disease or diabetes plus 1 risk factor. These were randomly allocated to receive either ramipril 10 mg/day or matching placebo. During a mean follow-up of 4.5 years there was a 21% relative reduction in the risk of clinically significant MI or cardiovascular death (95% CI, 11% to 30%, P=0.0003) with ramipril treatment. There was also a highly significant reduction in all-cause mortality, stroke, and the need for coronary revascularization.

Having already dramatically extended the potential use of ACE inhibition in secondary prevention, there was still no conclusive evi-
dence that ACE inhibition benefited a broader, lower-risk group of patients, who more accurately represented the existing patient population with established coronary heart disease. It was specifically to remedy this deficiency that the concept of EUROPA (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) was developed. The study was designed to assess the value of ACE inhibition in the prevention of cardiac events in lower-risk patients with stable coronary artery disease already on standard therapies. The ACE inhibitor perindopril was chosen for study on account of its lipophilic profile, sustained action in lowering blood pressure (a single dose providing 24-hour control), additional documented anti-ischemic and antiatherogenic actions, as well as its effect on cardiovascular remodeling: a multifactorial profile, which, in theory, might provide important benefit to the broad patient population selected for study.

A total of 12 218 patients aged between 26 and 89 (mean age 60 y) were recruited from 24 European countries. Patients were included on the basis of established CAD (defined as a previous MI at least 6 months earlier, surgery or revascularization, abnormal coronary angiography, or in men a positive exercise test) without evidence of heart failure. Over 80% of each group were male, 27% in each group were hypertensive, 12% were diabetic, 15% were smokers, and 63% had hypercholesterolemia. In terms of treatment, 92% were already taking a platelet inhibitor, 62% a β-blocker, 58% a statin, 32% a calcium channel blocker, and 44% a nitrate. Following a 4-week run-in period, they were randomized to receive either perindopril 8 mg/day (n=6110) or matching placebo (n=6108) for an average of 4.2 years.

For the combined primary end point, event rates were 9.9% (603 of 6108 patients) in the placebo group and 8.0% (488 of 6110 patients) in the perindopril group: a 1.9% absolute risk reduction and a 20% relative risk reduction (P=0.0003). In addition, perindopril reduced the secondary end point of total mortality, cardiovascular death, unstable angina, or cardiac arrest (P=0.0009) and also tertiary end points of fatal and nonfatal myocardial infarction (24%; P=0.001) and hospitalization for heart failure (39%; P=0.002). Benefits were present across all subgroups in men, women, older and younger patients, those with or without a history of prior MI, and those with or without diabetes, hypertension, or noncoronary vascular disease. Benefits were also seen regardless of whether or not other therapies such as statins and β-blockers were prescribed. All other tertiary end points showed a trend toward benefit, but did not achieve significance due to low event numbers in both treatment arms.

The Prevention of Events with Angiotensin-Converting Enzyme (PEACE) Investigators reported a negative outcome when comparing trandolapril 4 mg and placebo in patients with coronary artery disease. However, they wrongly state that their failure to demonstrate clinical benefits relates to an event rate that was “lower than the event rates in the ACE-inhibitor groups in (the) two previous trials.” Annualized all-cause mortality was similarly low in PEACE (1.6% per year) and EUROPA (1.5% per year) as compared with HOPE (2.3% per year). Furthermore, the annualized rate of occurrence of the combined primary end point for PEACE was higher than for either of the other two trials: PEACE (4.6% per year), HOPE (3.2% per year), and EUROPA (2.1% per year). It is also apparent that the event rates for cardiovascular death and nonfatal myocardial infarction are similarly low for PEACE (0.8% and 1.1% per year) and EUROPA (0.9% and 1.3% per year) as compared with HOPE (1.4% and 2.2% per year). These similarities in event rates are present despite significantly different baseline rates of lipid lowering and revascularization (PEACE 72% and 70%; EUROPA 58% [70% at 3 years follow-up] and 57%; HOPE 28% and 44%) and must have been also influenced by the mean baseline age of patients in the three trials (EUROPA 60 y, PEACE 64 y, and HOPE 66 y).

REGISTRY EVIDENCE FOR ACE INHIBITION

In the Evaluation of Methods and Management of Acute Coronary Events–1 (EMMACE-1) study performed in 1996, we sought to describe the pattern of ACE-inhibitor use for patients discharged from hospital after AMI, assessing the presence and magnitude of any discrepancies between actual and recommended practice. Potential cases of AMI were identified from coronary care unit (CCU) registers, biochemistry records of cardiac enzyme assay requests, and hospital management systems. A full-time research team then evaluated the hospital records of 3684 patients. The occurrence of AMI was confirmed in 2196 cases, of whom 1656 patients were discharged from hospital alive after a first event. The occurrence of either LV failure or systolic LV impairment and also discharge prescriptions of ACE-inhibitor therapy were documented and the survival status of all patients to 1st January 1998 was ascertained.

Patient characteristics

The average of age of patients with LV dysfunction in this cohort of consecutive patients discharged from
adjacent hospitals over the same time period was 72 years. This, coupled with the observation that 40% of our cohort were female, makes us believe that we have obtained data on a sample that is representative of routine clinical care. Attending physicians included generalists as well as specialists: 73% of patients were not cared for in a tertiary cardiac center and 27% were cared for outside of the CCU. While crude rates of thrombolysis (50%) and aspirin use at discharge (81%) were encouraging, statin (8%) and β-blocker (24%) use was low, reflecting prevailing beliefs over the time period studied. Nonmeasurement of LV systolic function (55%) probably reflected UK practice, particularly in the light of studies such as AIRE in which clinical criteria were used to target patients for ACE-inhibitor therapy. A 1-year mortality rate (from the time of hospital discharge) of 19% for patients with LV dysfunction was higher than is seen in most clinical trials of unselected patients though it was consistent with other epidemiological reports and the findings of studies such as AIRE that recruited patients with clinical heart failure.

ACE-inhibitor use

Of 1656 patients with confirmed AMI surviving to hospital discharge, 799 were categorized as having LV dysfunction based on documented evidence of either clinical LV failure or systolic LV impairment. The AIRE study entry criteria formed the basis of a diagnosis of LV failure, while the presence or absence of LV impairment was determined by echocardiography or radionuclear ventriculography. Patients without evidence of LV failure, in whom no measure of LV impairment had been performed, were considered to have no documented LV dysfunction. Of the 799 (100%) patients with documented LV dysfunction, 6 (0.8%) had no record of discharge medication. ACE-inhibitor therapy was not prescribed to 315 (39%) patients despite documented evidence of LV dysfunction, potential contraindications to ACE-inhibitor therapy being present in 87 (11%) and absent in 227 (28%) cases.

Treatment regimens

Of the LV dysfunction patients receiving ACE-inhibitor therapy at discharge, only 24% were prescribed a trial-recommended dose. This proportion of patients varied significantly with ACE-inhibitor subtype; captopril 4%, enalapril 16%, lisinopril 36%, ramipril 31% (P<0.001). Frequency of administration also varied significantly between different ACE-inhibitor subtypes (P<0.001); (Table I).

### Table I. EMMACE-1 study angiotensin-converting enzyme (ACE)-inhibitor regimens and associated 1 year mortality. Ratios are derived from Cox proportional hazards multivariate models including: (i) ACE inhibitor versus ACE inhibitor at discharge; (ii) no ACE inhibitor versus ACE inhibitor at less than trial target dose and ACE inhibitor at trial target dose; (iii) no ACE inhibitor versus sulphydryl ACE inhibitor (captopril) given less than 3 times daily; and (iv) no ACE inhibitor versus carboxyl ACE inhibitor (lisinopril, enalapril, or ramipril) given once daily and carboxyl ACE inhibitor given 2 times daily. The hazard ratio for patients with evidence either of left ventricular failure or systolic left ventricular dysfunction prior to hospital discharge not given ACE-inhibitor therapy was 1.00 in all analyses; 95% confidence interval is shown in all cases. *P<0.05.

<table>
<thead>
<tr>
<th></th>
<th>No ACE inhibitor (n=315)</th>
<th>Captopril (n=84)</th>
<th>Lisinopril (n=137)</th>
<th>Enalapril (n=141)</th>
<th>Ramipril (n=100)</th>
<th>Multivariate model relative hazard (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ACE inhibitor</td>
<td>100% (315)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.00</td>
</tr>
<tr>
<td>Nontarget ACE Target ACE</td>
<td>-</td>
<td>96% (81)</td>
<td>64% (81)</td>
<td>84% (118)</td>
<td>69% (69)</td>
<td>0.73 (0.49 to 1.07)</td>
</tr>
<tr>
<td>Sulphydryl ACE inhibitor</td>
<td>-</td>
<td>50% (42)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.74 (0.41 to 0.95)*</td>
</tr>
<tr>
<td>&lt; 3 doses/day</td>
<td>-</td>
<td>40% (34)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.64 (0.43 to 0.95)*</td>
</tr>
<tr>
<td>3 doses/day</td>
<td>-</td>
<td>-</td>
<td>89% (122)</td>
<td>50% (70)</td>
<td>28% (28)</td>
<td>0.76 (0.50 to 1.16)</td>
</tr>
<tr>
<td>ALL</td>
<td>-</td>
<td>-</td>
<td>5% (7)</td>
<td>46% (65)</td>
<td>70% (70)</td>
<td>0.37 (0.20 to 0.70)*</td>
</tr>
<tr>
<td>Carboxyl ACE inhibitor</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.64 (0.43 to 0.95)*</td>
</tr>
<tr>
<td>1 dose/day</td>
<td>-</td>
<td>-</td>
<td>89% (122)</td>
<td>50% (70)</td>
<td>28% (28)</td>
<td>0.76 (0.50 to 1.16)</td>
</tr>
<tr>
<td>2 doses/day</td>
<td>-</td>
<td>-</td>
<td>5% (7)</td>
<td>46% (65)</td>
<td>70% (70)</td>
<td>0.37 (0.20 to 0.70)*</td>
</tr>
<tr>
<td>ALL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.37 (0.20 to 0.70)*</td>
</tr>
<tr>
<td>Deaths</td>
<td>22% (70)</td>
<td>25% (21)</td>
<td>20% (28)</td>
<td>17% (24)</td>
<td>8% (8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Multivariate model relative hazard (95% CI)</td>
<td>0.69 (0.47 to 0.99)*</td>
<td></td>
<td></td>
<td></td>
<td>0.64 (0.43 to 0.95)*</td>
<td></td>
</tr>
</tbody>
</table>
“Real world” survival

Patients with LV dysfunction not prescribed an ACE inhibitor at discharge had a higher 1-year mortality than did those in whom an ACE inhibitor was prescribed (HR 1.32; 95% CI 0.96 to 1.92; P=0.086). This association was even more marked for patients with other traditional ACE-inhibitor selection criteria such as anterior Q-wave MI (2.07; 1.24 to 3.46; P=0.004) and the use of ongoing diuretic therapy (1.64; 1.15 to 2.43; P=0.005). Patients given an ACE inhibitor at a suboptimal total daily dose were observed to have a 1-year mortality rate (18.2%) that was higher than for patients receiving trial recommended daily doses though less than for those who received no ACE inhibitor. One-year mortality was 19.5% when contemporary contraindications to ACE inhibition were present (including no heart failure and preserved LV function), and 22.9% when no contraindications were present.

Adjusted survival

Because a decision not to prescribe an ACE inhibitor is likely to have been influenced by the presence of other prognostic factors, confounding of univariate measurement of survival is likely to have occurred. Consequently, we constructed a multivariate model including 18 baseline variables. Once again, patients with LV dysfunction not prescribed an ACE inhibitor at discharge had a significantly higher 1-year mortality risk than did those in whom an ACE-inhibitor regimen was prescribed (Figure 1: HR 1.46; 95% CI 1.00 to 2.11; P=0.048). This association was more marked in patients with other traditional selection criteria such as anterior Q-wave MI (2.19, 1.19 to 4.16, P=0.017) and the use of ongoing diuretic therapy (1.56, 1.03 to 2.38, P=0.038). As with univariate analysis patients given an ACE inhibitor at a suboptimal total daily dose were observed to have a 1-year mortality rate that was more than that seen for patients treated with a trial recommended dose of ACE inhibitor though less than for those receiving no treatment. Failure to prescribe an ACE inhibitor at any dose was independently predictive of a worse 1-year survival as compared with patients given a trial recommended total daily dose (HR 2.24; 95% CI 1.12 to 4.43; P=0.02).

ACE-inhibitor subtype and frequency

We extended our multivariate model to assess additional aspects of the therapeutic regimens prescribed. Sulphhydryl ACE inhibitor (captopril) as compared with no ACE inhibition (HR 0.74, 95% CI 0.41 to 1.34; P=0.33) and carboxyl ACE inhibitor as compared with no ACE inhibitor (HR 0.64, 95% CI 0.43 to 0.95; P=0.03) were both associated with a lower mortality though this achieved statistical significance only for the carboxyl subtype. We also evaluated trial-recommended frequencies of administration compared to no ACE inhibition and also lower frequencies of administration as compared with no ACE inhibition for both sulphhydryl and carboxyl subtypes (Table I). These data support the belief that dose and frequency of administration, together with selection of drug, are important in maximizing benefits.

“Class effect?”

Observing actual clinical practice in a time-window after the publication of all key trials, we and others have noted therapeutic shortfalls even for those patients for whom treatment indications are very clear. Importantly, few ACE inhibitors have been prospectively evaluated in patients after AMI with LV dysfunction or in patients with chronic LV dysfunction when remote from AMI. Consequently, equipotent regimens of ACE inhibitors in this
What is the best way to keep the RAS under control? - Hall and Kilcullen

Clinical situation are unclear. For example, the British National Formulary advises that lisinopril be given for prophylaxis after MI at a target dose of 10 mg od based on the GISSI-3 trial. Yet the optimal dose of this well-studied agent in patients with heart failure remains uncertain. It is widely assumed that all ACE inhibitors are able to reduce the mortality of cardiac patients to a similar degree. This is referred to as a “class effect.” However, such a belief assumes that equipotent regimens of these drugs are utilized. To date, no published evidence-base. Nevertheless, while EUROPA demonstrated a highly significant 20% relative risk reduction (95% CI 9 to 29%, \( P < 0.0003 \)) PEACE observed only 4% (95% CI -6% to 12%, \( P = 0.43 \)). Importantly, EUROPA studied 4000 more patients than did PEACE also opting to use a higher dose of a structurally similar ACE-inhibitor (perindopril 8 mg vs trandolapril 4 mg). The stated reason for selection of trandolapril 4 mg was the positive outcome seen for the TRACE trial that assessed survival oftrandolapril. HOPE patients may have also benefited from a higher dose of similar sized ACE-inhibitor molecule (ramipril 10 mg/day) and EUROPA patients from a higher dose of a smaller molecule (perindopril 8 mg/day).

**CONCLUSIONS**

Since the publication of the HOPE and EUROPA studies, many clinicians have opted to treat all patients long-term after MI irrespective of the presence or absence of randomized comparison of the effect of different ACE inhibitors on mortality has been performed. Nevertheless, the belief that all ACE inhibitors produce similar effects on survival, regardless of how they are actually prescribed, is also untenable.

The PEACE and EUROPA trials closed recruitment in the year 2000 being contemporary with regard to effects in patients after myocardial infarction that had an ejection fraction of less than 35%. Nevertheless, the likely target for treatment in PEACE was not circulating and accessible plasma ACE, but rather the large amounts of ACE expressed by macrophages located within the shoulder of atheromatous plaques. While drug penetration will have been aided by the lipophilic profile of cardiac dysfunction. Although both HOPE and EUROPA excluded patients with recent myocardial infarction, the consistent demonstration of a clear benefit from ACE-inhibitor therapy for patients with stable coronary artery disease supports a policy of routine use in patients with all forms of acute coronary syndrome (**Figure 2**). Nevertheless, contemporary, registry data\(^{10}\) indi-

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**Figure 2.** Spectrum of disease states for which angiotensin-converting enzyme (ACE)-inhibitor therapy has been shown to produce major survival benefits in randomized, placebo-controlled clinical trials.

**Abbreviations:** Angio, coronary angiogram; CABG, coronary artery bypass surgery; clin CCF, overt clinical congestive heart failure; DM, diabetes mellitus; ETT, exercise tolerance test; FH, family history of cardiovascular disease; LVEF, left ventricular ejection fraction; LVF, left ventricular failure; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
cater the presence of multiple short-falls between routine care and recommended practice based on the combination of direct (after MI) and indirect (in presence of CAD) trial data. Furthermore, the adverse consequences of these shortfalls seem clear. Consequently, there are a number of simple but important ways by which secondary prevention by modulation of the renin-angiotensin system might be improved. These include (i) wider routine use of appropriate ACE-inhibitor regimens (ramipril 10 mg daily; perindopril 8 mg daily) (ii) second-line use of the aldosterone antagonist eplerenone; and (iii) avoidance of ARBs (particularly losartan) in this setting.

4. GISSI-3 Investigators.
Six-month effects of early treatment with lisinopril and transluminal glyceryl trinitrate singly and together withdrawn six weeks after acute myocardial infarction.

Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial.

A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction.

Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure.

8. Hall AS, Murray GD, Ball SG.
Follow-up study of patients randomly allocated ramipril or placebo for heart failure after myocardial infarction: AIREX Extension (AIREX) study.

Mechanisms behind the prognostic value of troponin T in unstable coronary artery disease: a FRISC II substudy.

ACE inhibitor use in patients with myocardial infarction. Summary of evidence from clinical trials.


12. The Task Force of the Working Group on Heart failure of the European Society of Cardiology.
*Eur Heart J.* 1997;18:736-753.

13. Dickstein K, Kfekshus J.
Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial.

Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both.

Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial: the Losartan Heart Failure Survival Study ELITE II.

Angiotensin II receptor-independent anti-inflammatory and antiaggregatory properties of losartan: role of the active metabolite EXP3179.

17. Sadoshima J.
Novel AT1 receptor-independent functions of losartan.

18. LIFE Investigators.
Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reDuction in hypertension study (LIFE): a randomised trial against atenolol.

**REFERENCES**

Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II).

Oral captopril versus placebo among 13,634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1).

3. ISIS-4 Collaborative Group.
Fourth International Study of Infarct Survival. A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 38,650 patients with suspected acute myocardial infarction.
19. Verma S, Strauss M. Angiotensin receptor blockers and myocardial infarction. These drugs may increase myocardial infarction—and patients may need to be told. BMJ. 2004;329:1248-1249.


How best to keep the sympathetic nervous system under control in coronary artery disease?

Claudio Ceconi, MD, FESC

Prof Claudio Ceconi - Cattedra di Cardiologia - Università degli Studi di Ferrara - Ferrara - ITALY

There are clear pathophysiological grounds for modulating the sympathetic nervous system in coronary artery disease. The tools are primarily pharmacologic: β-blockers have been validated in multiple prospective controlled trials and are now recommended on the basis of the best possible evidence by numerous cardiology societies in many settings; their use benefits virtually all patients and has multiple targets. Trials with newer agents, eg, ivabradine, are ongoing. The main nonpharmacologic approach is comprehensive cardiac rehabilitation: exercise programs directly impact major risk factors for cardiac death, such as heart rate variability. However, the quality of guideline implementation fails to match the quality of the supporting evidence: fewer than half of eligible patients actually receive the recommended therapies. Closing this gap is now the main challenge for clinicians.

Understanding the mechanisms and pathophysiology of sympathetic nervous system (SNS) involvement in the progression of coronary artery disease (CAD) generally is essential for effective secondary prevention, in particular because the SNS has attracted much less attention in this setting than, for instance, after acute myocardial infarction (MI), where β-blockers now have a well-recognized role.

SNS inhibition can influence progression and outcome in CAD through a variety of mechanisms:

- Risk factor control, in particular by lowering blood pressure,
- Decreased adrenergic burden on the heart due to decreased sympathetic drive (catecholamines are toxic to cardiomyocytes, even at the concentrations commonly associated with environmental stress and heart disease)
- Prevention of ventricular arrhythmias and sudden death through modulation of sympathetic/parasympathetic balance and the catecholamine effect on intrinsic cardiac electrophysiology
- Enhanced plaque stability and blood rheology, due to decreased vessel wall stress from the negative inotropism induced by the decreased sympathetic drive.

Despite such potential benefits in both personal and public health terms, the tools for controlling the SNS are relatively few. Pharmacologic approaches have changed little in their fundamentals for many decades, in striking contrast with paradigm shifts in other therapeutic fields. This article reviews the available tools and current understanding of SNS modulation in secondary CAD prevention.

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASIST</td>
<td>Atenolol Silent Ischemia STudy</td>
</tr>
<tr>
<td>CAPRICORN</td>
<td>Carvedilol Post Infarction Survival Control in Left Ventricular Dysfunction</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>SNS</td>
<td>sympathetic nervous system</td>
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**PHARMACOLOGIC INHIBITION OF THE SYMPATHETIC NERVOUS SYSTEM**

**β-Blockers**

β-Blockade has been a major advance in the treatment of CAD because it prevents not only angina, but also new events. It does so by mechanisms that differ according to the ischemic syndrome concerned, as explained below.
Myocardial infarction

Yusuf et al appraised the efficacy of β-blockade during and after MI in a major overview of some 65 randomized trials in 1985. Subsequent evidence has only strengthened this conclusion. Large long-term trials in a total of over 35,000 survivors of MI have shown that β-blockade improves survival by 20% to 25% through decreases in cardiac mortality, sudden death, and reinfarction.

The effective β-blockers in this regard are propranolol, metoprolol, timolol, and acebutolol; no benefit versus placebo is shown by alprenolol, oxprenolol, xamoterol, or pindolol. Although often used in secondary prevention, atenolol has not yet been adequately evaluated in this setting, nor are any long-term trials in unselected patients available for carvedilol. However, in the Carvedilol Post Infarction Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial in patients receiving angiotensin-converting enzyme (ACE) inhibitors, carvedilol reduced the frequency of recurrent nonfatal MI and all-cause and cardiovascular mortality.

A recent meta-analysis of β-blockade in secondary prevention after MI included all 82 randomized studies conducted between 1966 and 1999 in a total of 54,234 patients (10.1% deaths). Follow-up was ≤6 months (“short-term”) in 51 of the studies and >6 months (“long-term”) in the remainder. The short-term studies showed only a 4% reduction in the odds of death (95% confidence interval [CI]: –8% to 15%, Figure 1), equivalent to just 1 death per 250 patients, which was not significant. The long-term studies, on the other hand, showed a 23% reduction in the odds of death (CI: 15% to 31%, Figure 2), meaning that 84 patients would require treatment for 1 year to prevent 1 death. This figure compares favorably with the mortality benefit conferred by antiplatelet agents, warfarin, and statins after MI. There was no evidence of additional benefit from an initial intravenous dose. Meta regression in the long-term studies identified a near significant trend towards decreased benefit from drugs with

<table>
<thead>
<tr>
<th>Trial</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol pooled</td>
<td>74.2</td>
<td>0.93 (0.85 to 1.02)</td>
</tr>
<tr>
<td>Labetalol pooled</td>
<td>0.4</td>
<td>1.84 (0.62 to 5.51)</td>
</tr>
<tr>
<td>Metoprolol pooled</td>
<td>11.2</td>
<td>0.88 (0.70 to 1.11)</td>
</tr>
<tr>
<td>Oxprenolol pooled</td>
<td>2.4</td>
<td>1.30 (0.82 to 2.05)</td>
</tr>
<tr>
<td>Pindolol pooled</td>
<td>0.1</td>
<td>1.00 (0.01 to 80.08)</td>
</tr>
<tr>
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<td>2.0</td>
<td>1.23 (0.74 to 2.04)</td>
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<tr>
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<td>1.00 (0.77 to 1.28)</td>
</tr>
<tr>
<td>Timolol pooled</td>
<td>1.0</td>
<td>0.72 (0.32 to 1.60)</td>
</tr>
<tr>
<td>Fixed effects pooled</td>
<td>100</td>
<td>0.95 (0.88 to 1.02)</td>
</tr>
<tr>
<td>Full random effects pooled</td>
<td>100</td>
<td>0.96 (0.85 to 1.08)</td>
</tr>
</tbody>
</table>

Heterogeneity Q=21.0, df=50, P=1.0

Figure 1. Pooled odds of death ratios in short-term trials with a single β-blocker (see text).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
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<td>0.49 (0.25 to 0.93)</td>
</tr>
<tr>
<td>Alprenolol pooled</td>
<td>6.6</td>
<td>0.83 (0.59 to 1.17)</td>
</tr>
<tr>
<td>Atenolol pooled</td>
<td>1.6</td>
<td>1.02 (0.52 to 1.99)</td>
</tr>
<tr>
<td>Carvedilol pooled</td>
<td>0.3</td>
<td>0.62 (0.05 to 6.11)</td>
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<tr>
<td>Metoprolol pooled</td>
<td>23.1</td>
<td>0.80 (0.66 to 0.96)</td>
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<td>Oxprenolol pooled</td>
<td>11.8</td>
<td>0.91 (0.71 to 1.17)</td>
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<td>Pindolol pooled</td>
<td>3.6</td>
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</tr>
<tr>
<td>Full random effects pooled</td>
<td>100</td>
<td>0.77 (0.69 to 0.85)</td>
</tr>
</tbody>
</table>

Heterogeneity Q=49.7, df=32, P=0.16

Figure 2. Pooled odds of death ratios in long-term trials with a single β-blocker (see text).
How best to keep the sympathetic nervous system under control in CAD? - Ceconi

intrinsic sympathomimetic activity, which should therefore be avoided. The meta-analysis was also noteworthy for showing no evidence that the availability of new treatments such as pharmacologic thrombolyis and aspirin decreases the benefit of β-blockade.

These results confirmed those of the Cooperative Cardiovascular Project in 201,752 post-MI patients. Mortality was lower in every subgroup treated with β-blockers, including those with comorbidities once considered as contraindications, e.g., chronic pulmonary disease, low ejection fraction and older age. In particular, β-blockade decreased mortality in the lowest-risk subgroups by 40%, suggesting that withholding β-blockers from patients with a favorable prognosis (young age, intact left ventricular function, no residual ischemia or ventricular arrhythmia), as advocated by some, may be a misguided strategy. Absolute benefit may well be lower in these low-risk patients, but their survival is indubitably increased. The subgroups with most to gain from β-blockade, on the other hand, include diabetics (in whom chronic pulmonary disease is more conclusive in stable angina. Although the full complexity of their impact on autonomic and cardiovascular function is still largely unelucidated, β-blockers are effective after acute MI in preventing sudden death and, possibly, in preventing/treating late ventricular arrhythmias (Table I).5,18

### Sudden death
Sympathetic overactivity is associated with unstable angina and is particularly intense after MI.17 For reasons that remain disputed, the ischemic heart is a powerful site of origin of excitatory and/or inhibitory reflexes; indeed, it is likely that both sets of reflexes are usually activated simultaneously, although one eventually prevails. Sympathetic overactivity depresses baroreflex function18 and can be a major determinant of cardiac accidents, including sudden death.2

#### Setting/Indication

<table>
<thead>
<tr>
<th>Setting/Indication</th>
<th>Class</th>
<th>Level</th>
</tr>
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<tbody>
<tr>
<td><strong>After acute myocardial infarction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients without contraindications, indefinitely</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>To improve survival</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>To prevent reinfarction</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Primary prevention of sudden death</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>To prevent/treat late ventricular arrhythmias</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td><strong>In non-ST-segment elevation acute coronary syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term secondary prevention</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td><strong>In chronic, stable ischemic heart disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To improve survival</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>To reduce reinfarction</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

*Table 1. β-Blockade in secondary prevention: European Society of Cardiology guidelines.*


Expert guidelines recommending routine long-term β-blockade after MI are based on class I evidence, level A, of decreased mortality and morbidity (Table I).4 Yet under half of eligible patients actually receive this treatment.11-13 Although there is some evidence that adverse events and side effects with β-blockers are more frequent than previously thought, recent major systematic reviews show no increase in depression and only a slight increase in fatigue and sexual dysfunction,15,14 while asthma and chronic obstructive pulmonary disease are no longer viewed as mandatory contraindications.15

**Non-ST-segment elevation ACS and chronic stable ischemic heart disease** In acute coronary syndromes (ACS), it is clearly difficult to differentiate the early benefit of β-blockade due to decreased ischemia and/or prevention of MI, from the long-term benefit due to secondary prevention. Trials in this setting have been few and sample sizes small. The evidence favoring β-blockade for preventing MI and prolonging survival is more conclusive in stable angina. The Beta-Blocker Pooling Project reported a highly significant reduction in mortality in post-MI stable angina, and it seems reasonable to assume that β-blockers prevent death and MI even in the absence of prior MI (Table I).9 In the Atenolol Silent Ischemia SStudy (ASIST), atenolol decreased ischemic episodes at 6 weeks and improved event-free survival at 1 year versus placebo.16 Although the full complexity of their impact on autonomic and cardiovascular function is still largely unelucidated, β-blockers are effective after acute MI in preventing sudden death and, possibly, in preventing/treating late ventricular arrhythmias (Table I).5,18

Their use should therefore be regarded as mandatory in acute MI, the post-MI phase and also in congestive heart failure.
Other pharmacologic treatments

Several other antiadrenergic classes of drugs are available, but none have been validated for use in secondary prevention. Central antiadrenergic drugs (eg, clonidine) do not offer significant protection, nor are they first-line treatments for hypertension, while other compounds such as reserpine and guanfacine are no longer used. No pilot study is available to support the possible use of these agents, nor is there any preclinical study to suggest they may be useful in cardiovascular prevention.

An interesting approach to the treatment of essential hypertension is provided by imidazoline agonist agents such as rilmenidine. This agent binds to specific I1 imidazoline receptors in the brain stem and kidney and reduces the sympathetic overactivity associated with hypertension. Rilmenidine has a better tolerability profile than \(\alpha_2\) agonists (clonidine, \(\alpha\)-methyldopa). In the presence of metabolic disorders (dyslipidemia, metabolic syndrome, type 2 diabetes), in contrast to \(\beta\)-blockers, rilmenidine improves lipid parameters, insulin sensitivity, and plasma glucose concentrations. Rilmenidine has also been shown to reduce left ventricular hypertrophy in patients with hypertension. Further trials are necessary to determine rilmenidine’s value in secondary prevention.

Newer drugs promise greater potential. Ivabradine, a specific blocker of the cardiac pacemaker (\(I_f\)) current, is a novel selective heart rate–reducing agent with no negative inotropic and no effect on atrioventricular conduction or ventricular depolarization. Developed as a treatment of stable angina, it lowers the heart rate and double product, thereby decreasing cardiac workload and myocardial oxygen consumption. In mice, oral ivabradine reduces the heart rate without affecting ventricular performance. Ivabradine even continues to lower the heart rate in the face of conditions associated with significant SNS activation, including stress, cardiac-restricted overexpression of \(\beta_2\)-adrenergic receptors, and \(\beta\)-agonist administration. Clinical trials to determine its usefulness in secondary prevention are ongoing.

NONPHARMACOLOGIC INHIBITION OF THE SNS: CARDIAC REHABILITATION

Environmental factors are critical to SNS balance. Stress control and enhanced psychological adjustment to illness are major targets in cardiac rehabilitation strategy designed to modulate the SNS. Insofar as its overall aims are to optimize patient function, enhance quality of life, and minimize the risk of recurrence, cardiac rehabilitation is integral to, and overlaps with, secondary prevention. Its programs comprise exercise training, behavioral changes, education, and psychological support. Some of the mechanisms involved directly impact the SNS: exercise training strengthens the parasympathetic component in sympathovagal balance, resulting in increased heart rate variability, protection against malignant arrhythmia, lower myocardial wall stress, and long-term myocardial protection. Exercise also affects the natural history of atherosclerotic lesions by improving endothelial dysfunction; nitric oxide directly scavenges norepinephrine, a vasoconstrictor and an index of SNS overactivity. A 2001 Cochrane review showed a 27% reduction in mortality with exercise alone or exercise as part of a comprehensive cardiac rehabilitation strategy, while Hambrecht et al recently published the striking finding that a program of regular physical exercise in selected patients with stable CAD produced superior event-free survival and exercise capacity than percutaneous coronary intervention, and at lower cost.

REFERENCES


How best to keep the sympathetic nervous system under control in CAD? - Ceconi


What is the best way to manage dyslipidemia?

Jim Shepherd, MD, PhD
Institute of Biochemistry - Royal Infirmary - Glasgow - UK

The processes involved in discovering, developing, and testing new drugs often focus on detailed refinement of chemistry or engineering practice, which result in small, albeit clinically valuable, improvements in the management of a particular disease state. But just occasionally, either through serendipity or insightful creativity, or both, a series of new compounds comes to light whose uniqueness of action revolutionizes the management of a hitherto intractable clinical problem. Such was the case when pharmacology unveiled the wide-ranging portfolio of lipid-lowering agents, which for the first time has allowed us to control the worst excesses of dyslipidemia in our patients. Here we consider the discovery and review the clinical merits of the statins, ezetimibe, the peroxisome proliferator activated receptor (PPAR) agonists, and nicotinic acid.

DISCOVERY OF THE ULTRACENTRIFUGE

Theodor Svedberg (1884-1971) won the Nobel Prize for Chemistry in 1926 for his studies of colloids.1 His early research on these particles showed that they were not only too small to be seen by conventional light microscopy, but that jostling by surrounding water molecules prevented their precipitation by gravity. High centrifugal forces were therefore required to mimic the effects of gravity on them. This realization led to his construction of the first ultracentrifuge in 1924, a machine that in its time was capable of generating a force of up to 5000 times the force of gravity. Subsequent refinements led to the development of instruments that could apply gravitational fields to colloids so that discrimination could be made between them on the basis of their mass. So, with the advent of the ultracentrifuge, our ability to determine the molecular weights of highly complex particles like proteins became a reality.

IDENTIFICATION OF LIPOPROTEINS

The second ultracentrifuge that appeared in the United States (the first went to Melvin Calvin) was delivered to the Donner Laboratories in Berkeley, California in the early 1950s. John Gofman, Frank Lindgren, and their collaborators immediately pressed it into service to look at serum proteins, despite the strictures of Kai Pedersen that serum protein analysis might defeat them (“there’s some unstable molecules in the serum and you can get any result you want from the ultracentrifuge—don’t try to do it with blood”). Pedersen’s early predictions were indeed vindicated by depressing findings. While most serum proteins (whose particle density was approximately 1.34 g/mL) were precipitated by ultracentrifugation, some seemed to float in the gravitational field. Frank Lindgren’s fertile mind ultimately resolved this dilemma. He conjectured that while most proteins existed free in serum and so were sedimented by the ultracentrifuge, some might be so intimately related to other molecules in solution that, contrary to expectation, they actually float in high gravita-
tional fields. The concept of lipid-protein complexes or lipoproteins had come of age. The logical extension of these studies was not only to define lipid-protein complexes in the serum, but also to classify them into particles of very low, low, and high density (now known as very-low-density [VLDL], low-density [LDL], and high-density [HDL] lipoproteins).

VASCULAR RISK FACTORS DEFINED

Epidemiological studies, pioneered by the Framingham Project, capitalized on the discovery of the lipoproteins to show that while increased concentrations of HDL in the bloodstream led to protection against coronary heart disease (CHD—the most important global cause of death both then and now), circulating LDL predisposed to it. The teamwork of Joseph Goldstein and Michael Brown in Dallas, Texas, and their intuitive concerns over the relevance of an inherited form of hypercholesterolemia (defined by Carl Mueler in Oslo as an inherited disease caused by a defect in an autosomal gene and later identified by Khachadurian in the Lebanon as occurring in a mild (heterozygous) and severe (homozygous) form of condition that we now know as familial hypercholesterolemia) ultimately shed light on the role of LDL in the pathogenesis of atherosclerosis. Using cell culture techniques they showed that, whereas cells from healthy individuals expressed proteins on their surface membranes (LDL receptor proteins) that could recognize, bind, and assimilate LDL from the surrounding culture medium, individuals with familial hypercholesterolemia suffered from partial or complete absence of functional LDL receptors. As a consequence, LDL cholesterol levels in their blood were significantly higher than normal, and thus led to a substantial increase in their risk of developing atheromatous occlusion of their arterial tree, and of ultimately succumbing to coronary and peripheral arterial disease and stroke. So, the efficient operation of these LDL receptors appeared to be a prerequisite to the avoidance of occlusive atherosclerosis.

PENICILLIN FOR THE HEART—THE DEVELOPMENT OF THE STATINS

While Goldstein and Brown were working their way toward the Nobel Prize in Physiology or Medicine in 1985 “for their discoveries concerning the regulation of cholesterol metabolism,” another researcher, Akira Endo, employed by the Sankyo Pharmaceutical Company in Tokyo, put his mind to the identification and manufacture of a fungal metabolite capable of blocking cellular cholesterol production by inhibiting the rate-limiting enzyme involved in the cholesterol synthetic pathway, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. His discovery, compactin, when given to experimental animals, blocked cholesterol synthesis in their liver and led to upregulation of the expression of LDL receptors on hepatocyte membranes. As a result, LDL was extracted from their circulation and plasma cholesterol levels fell through activation of what was in effect a physiological pathway (Figure 1). Subsequent modification of this progenitor compound resulted in the delivery to the clinic of a family of cholesterol-lowering

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**Figure 1.** Mechanism of action of statins. By inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme for cholesterol synthesis in the liver, the statins deprive hepatocytes of their sterol source. This is restored by activation of low-density-lipoprotein (LDL) receptors on the hepatocyte membrane, which extract LDL from the circulation and, in consequence, lower plasma LDL levels.
251 molecules (the statins), which have revolutionized our ability to decrease plasma cholesterol levels and, as a result, have had a clinical impact, which some believe “is to atherosclerosis what penicillin (the original fungus-derived antibiotic) was to infectious disease.” However, the prime lesson that emerged from our use of antibiotics is that Nature is not as easy to tame as we might imagine, and some are beginning to hint at the same conclusions about statins and CHD prevention. If these agents really lived up to expectation, they say, surely coronary events would have been eliminated rather than “merely” reduced by 30% to 50%. But of course, despite the runaway successes of statin-based end point trials, no clinical study of this kind can truly reflect the multifaceted biology of real life, and to eliminate a disease whose origins go back to childhood we no doubt will need to take action over a longer time frame than that dictated by the exigencies of clinical trial design.

**SPECIFIC INHIBITION OF CHOLESTEROL ABSORPTION**

Another important mechanistic issue needs also to be considered. Corporeal cholesterol homeostasis depends on the balance between endogenous cholesterol production (principally in the liver) and intestinal absorption of the sterol from the diet and the enterohepatic circulation. Suppression of endogenous cholesterol production by statins does nothing to inhibit the absorption of exogenous sterol and can therefore only be expected to be partially effective in reducing plasma cholesterol levels. What we clearly need to do is simultaneously inhibit endogenous synthesis and exogenous absorption. Statins effectively deliver the former while the recently identified drug, ezetimibe, is equally able to provide the latter (Figure 2).

Ezetimibe was approved for clinical use in Europe and the USA in October 2002. It is virtually water insoluble but, following ingestion, is rapidly glucuronidated in the small intestine and liver. The glucuronides constitute 90% of the drug found in the plasma and show greater potency than the native drug with regard to inhibition of cholesterol absorption. Both the native and glucuronidated compound are largely sequestered within and recycle through the enterohepatic circulation, thereby repeatedly delivering active agent to its therapeutic target in the small intestine. Ezetimibe binds selectively to an as yet unknown structure (tentatively identified as the Niemann-Pick C-1–like 1 protein) on the villous brush border of the upper jejunum, where it inhibits the absorption of cholesterol and related plant sterols. Because of its selective ability to inhibit intestinal cholesterol absorption, it is an ideal partner for the statins, which block hepatic sterol production. When these drugs are combined, ezetimibe produces an additional 20% reduction in LDL cholesterol so that its coprescrip-
tion with statins at their lowest dose results in the same cholesterol reduction as would be achieved by the maximum dose of the statin in monotherapy (Figure 3). Since intensive lipid-lowering therapy with statins in patients with stable coronary heart disease provides significant clinical benefit beyond that seen with moderate intervention,12,13 this low-dose statin/ezetimibe combination may therefore, in terms of safety, be an alternative option in situations where profound cholesterol reduction is required.

**STATINS AT THEIR ZENITH**

Statins have revolutionized the management of hypercholesterolemia and rightly dominate the lipid-lowering drug field. However, the recent global launch of the “super statin” rosuvastatin and the evident success of aggressive LDL cholesterol lowering with atorvastatin 80 mg in the Treating to New Targets (TNT) study means that the market for this new class of drugs is not only becoming crowded, but may also have reached its maximal clinical potential. Alternative scenarios for resetting the atherogenic profile of the circulating lipoproteins need to be addressed. Within this framework, raised triglyceride and low HDL cholesterol are assuming increasing prominence, reawakening interest in well-established agents like the fibrates and nicotinic acid and driving forward the enthusiastic development of selective HDL cholesterol–enhancing compounds like the cholesteryl ester transfer protein (CETP) inhibitors.

Low plasma concentrations of HDL cholesterol and elevated triglyceride characterize patients with diabetes or the metabolic syndrome, both of which groups are at markedly increased risk of developing and dying from cardiovascular disease.14,15 Although LDL cholesterol in insulin-resistant patients is commonly normal or only modestly elevated, the characteristics of these cholesterol-containing particles are profoundly changed so that their size is reduced, their density raised, and their atherogenicity accentuated. Simultaneous and similar changes appear to occur in HDL, which not only becomes smaller and denser, but is also impaired in its ability to participate in reverse cholesterol transport and to protect LDL against endogenous oxidation.

Current treatment recommendations for the management of diabetic/metadata metabolic syndrome dyslipidemia focus on statins, even although plasma LDL cholesterol levels are usually only marginally (if at all) elevated in these patients. The driver behind this policy is the major statin trial outcomes, which demonstrated the benefits of reductase inhibition in these populations, even although they were only a subset of the entire statin trial portfolio. But, while there is no doubt that statins significantly reduce the risk of coronary heart disease in insulin-resistant patients, subgroup analysis from the Heart Protection Study (HPS)16 showed that the residual risk of a coronary event in diabetic patients remained twice as high as that in nondiabetics who got statins (Figure 4). So, although diabetic patients gained as much proportionately as nondiabetics, in absolute terms, treatment did not reduce their absolute risk to the same extent as in nondiabetics. These findings were concordant in all statin trials, irrespective of the statin involved. So, clustering of risk factors in insulin-resistant individuals increases their propensity to CHD and limits their statin-derived benefit.

**LDL cholesterol is the primary target of statin therapy, whose effects on triglyceride-lowering (15% to 25%) and HDL cholesterol raising (typically less than 10%) are considerably more modest. Even aggressive statin therapy with atorvastatin or rosuvastatin will improve little**
What is the best way to manage dyslipidemia?

Consequently, there is a growing realization that, despite the gold-standard status of the statins, additional therapy may be required to deal with low HDL cholesterol and elevated triglycerides, both of which are not only common, but also appear to substantially increase the burden of cardiovascular risk. Among all of the lipid risk factors, which influence coronary heart disease, HDL cholesterol is preeminent and is clearly established as independently predictive in both diabetic and nondiabetic individuals. Several trials have helped to establish its importance in this regard, including the Veterans Affairs High-density lipoprotein Intervention Study (VA-HIT)\(^\text{17}\) and the Helsinki Heart Study (HHS).\(^\text{18}\)

In both, the individuals who gained most from gemfibrozil intervention were those with initially low HDL, raised triglyceride, and a predisposition to insulin resistance. Consequently, it seems logical to develop the concept of combining the LDL-lowering benefits of a statin with agents that specifically promote HDL cholesterol elevation and triglyceride lowering.

### Strategies for Raising HDL Cholesterol and Lowering Plasma Triglyceride

Lifestyle modifications such as weight reduction coupled with initiation of an exercise program and elimination of cigarette smoking will all produce a significant, sustained improvement in plasma triglyceride and circulating HDL cholesterol and should be part of all CHD risk-reduction programs. However, in order to reach the required HDL targets, particularly in patients with diabetes or the metabolic syndrome, additional supportive therapeutic strategies are often required. These include the prescription of peroxisome proliferator activated receptor (PPAR) agonists (\(\alpha\) and \(\gamma\)) and nicotinic acid. Newer drugs like the CETP inhibitors show a lot of promise, but have not yet been established in clinical practice.

### PPAR\(\alpha\) Agonists

The fibrates, the progenitor PPAR\(\alpha\) agonists (the most popular of which are fenofibrate, bezafibrate, and gemfibrozil) reduce triglyceride by 20% to 50%, lower LDL cholesterol by 5% to 20%, and raise HDL cholesterol by 10% to 15%, depending on the drug in question and the baseline lipid profile of the recipient.\(^\text{19}\)

Several trials, the most recent of...
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which is VA-HIT, have established the merit of such intervention in CHD prevention. Gemfibrozil administration in VA-HIT reduced CHD death and nonfatal myocardial infarction by 22% (P=0.006) over a five year treatment period.\(^1^7\) So, fibrate therapy seems to be a viable adjunct to statins\(^2^0\) (Table I), particularly in patients with raised triglyceride, low HDL cholesterol, and “average” LDL cholesterol, the kind of patient who commonly appears with the metabolic syndrome or diabetes. As a consequence of this, cogent argument has been raised for combining fibrates with statins in individuals with combined dyslipidemia (raised triglyceride and LDL cholesterol and low HDL cholesterol). However, we do not know enough about the relative merits and risks of such a combination to recommend it unreservedly.

### Table 1. Some actions of peroxisome proliferator-activated receptor–α (PPARα) agonists.

**Abbreviations:** CRP, C-reactive protein; FFA, free fatty acids; TNFa, tumor necrosis factor–α.

<table>
<thead>
<tr>
<th>Major impact on hepatocyte gene expression</th>
<th>Target genes participate primarily in lipid catabolism</th>
<th>May be anti-inflammatory</th>
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<tbody>
<tr>
<td>- FFA translocation into hepatocytes</td>
<td>- FFA oxidation in microsomes, peroxisomes, and mitochondria</td>
<td>- Inhibit cytokine (TNFa and interleukin) production</td>
</tr>
<tr>
<td>- FFA oxidation in microsomes, peroxisomes, and mitochondria</td>
<td>- Lipoprotein assembly, secretion, and metabolism</td>
<td>- Decrease CRP and fibrinogen</td>
</tr>
<tr>
<td>- Lipoprotein assembly, secretion, and metabolism</td>
<td>- May be anti-inflammatory</td>
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across the board. Certainly, the combination gives significantly greater triglyceride and LDL cholesterol reduction than either agent alone, although its HDL cholesterol-raising properties are perhaps not ideal, and there is serious concern about combining gemfibrozil with any statin following the unexpected and catastrophic interactions observed between this fibrate and cerivastatin. Fenofibrate and bezafibrate in combination with statins do not seem to carry this risk, and further analysis of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial\(^2^0\) may help reassure us on that score.

### PPARγ AGONISTS

The PPAR\(γ\) agonists exemplified by the thiazolidinediones like rosiglitazone and pioglitazone, are active in the management of abnormalities of fat and carbohydrate metabolism, and are indicated for the treatment of diabetes mellitus (Figure 5). Of the two, pioglitazone appears to be more potent as a lipid-modulating agent, raising HDL cholesterol by about 10% and lowering triglyceride by 18% to 20%.\(^2^1\) Both drugs also exhibit a range of anti-inflammatory properties. Rosiglitazone, for example, reduces the plasma level of the inflammatory marker C-reactive protein (CRP), lowers the activity of matrix metalloproteinase 9 (MMP-9) in the circulation, and suppresses the production of proinflammatory cytokines by adipose tissue. These effects may help stabilize the atherosclerotic plaque,\(^2^2\) although this yet remains to be established, as have the safety and efficacy of these agents in the long-term management of vascular risk. No long-term studies of thiazolidinediones/statin combinations have been published so far.

### NICOTINIC ACID

Nicotinic acid is a long-standing lipid-lowering agent, which reduces triglyceride and LDL cholesterol by about 50% and 25%, respectively, and raises HDL cholesterol by as much as 30% at the doses recommended in the clinic.\(^2^3^,^2^4\) Its powerful effect on triglyceride (Figure 6) is also instrumental in increasing the average size of LDL and HDL particles in the circulation, thereby significantly reducing the atherogenicity of the plasma lipoprotein profile.\(^2^4^,^2^5\) It is therefore not surprising that in the Coronary Drug Project, an early investigation of
the potential of nicotinic acid, the drug not only lowered the risk of myocardial infarction, but also, over the long term, extended life.

Combining nicotinic acid with a statin is not only logical, but also therapeutically advantageous. Pro-longed-release nicotinic acid coadministered with lovastatin (in doses of 1000 mg and 20 mg, respectively) lowered LDL cholesterol and raised HDL cholesterol by 32% and 17%, respectively26, and similar changes induced by a nicotinic acid/simvastatin combination in the High-density lipoprotein Atherosclerosis Treatment Study (HATS)27 drove a significant improvement in coronary angiography and a 90% fall in the frequency of major coronary events compared with placebo ($P=0.03$) in patients with established CHD. Currently, there is no clear consensus as to which is the most appropriate statin for use with nicotinic acid, although it is noteworthy that a fixed combination tablet of extended-release nicotinic acid with lovastatin (Figure 7) has just become available in the United States.28 Nicotinic acid/simvastatin combination may be more appropriate in Europe since this statin has now lost patent protection (and lovastatin is not widely available) across the Continent.

**SUMMARY**

- The wide-ranging portfolio of benefit that has been established for the statins makes these agents the drugs of choice in patients with hypercholesterolemia and at risk of a first or repeat vascular event.
- Diabetics also benefit from such intervention, although even on treatment their vascular risk remains substantially elevated. Addition of a fibrate or nicotinic acid may improve the risk profile, although this remains to be established in the crucible of a clinical end point trial.
- Patients with hypertriglyceridemia and low HDL cholesterol merit intensive lifestyle advice and appropriate intervention. Current evidence suggests that fibrates or nicotinic acid may be of value in this situation, based on a growing portfolio of clinical trial evidence.
What is the best way to manage dyslipidemia? - Shepherd

REFERENCES

1. No authors listed.
   Theodor Svedberg; 1926 Nobel Laureate in Chemistry.
   http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1926/

2. Gofman JW, Glazier F, Tamplin A, Strisower B, de Lalla O.
   Lipoproteins, coronary heart disease and atherosclerosis.
   Physiol Rev. 1954;34:589-607.

3. Gordon T, Castelli WP, Hjortland MC, Kannel WB.
   The prediction of coronary heart disease by high density and other lipoproteins: an historical perspective. In: Rijks BM and Levy RI, eds.

4. Brown MS, Goldstein JL.

5. Roberts WC.
   The underused miracle: the statin drugs are to atherosclerosis what penicillin was to infectious disease.


7. Shepherd J.

   Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia.

   Efficacy and safety of ezetimibe coadministered with pravastatin in primary hypercholesterolemia: a prospective, randomized, double-blind trial.

    Ezetimibe coadministered with simvastatin in patients with hypercholesterolemia.

    Effects of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia.

    Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes.

    Intensive lipid lowering with atorvastatin in patients with stable coronary disease.

    Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction.

    Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease and all causes in the United States.

    MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial.

    Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of HDL cholesterol.

    Helsinki Heart Study: primary prevention trial with gemfibrozil in middle aged men with dyslipidemia.

19. Chapman MJ.

    Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD Study): randomized controlled trial.

    Thiazolidinediones and blood lipids in type 2 diabetes.


23. Elam MB, Hunninghake DB, Davis KB, et al.
    Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease.

    Extended-release nicotinic acid versus gemfibrozil for the treatment of low levels of HDL cholesterol.
    Niaspan-Gemfibrozil Study Group.


25. Superko HR, Krauss RM.  
Differential effects of nicotinic acid in subjects with different LDL subclass patterns.  
_Atherosclerosis_. 1992;95:69-76.

Efficacy of extended release niacin with lovastatin for hypercholesterolemia: assessing all reasonable doses with innovative surface graph analysis.  

Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease.  

28. Kashyap ML, McGovern ME, Berra K et al.  
Long-term safety and efficacy of a once-daily nicotinic acid/lovastatin formulation for patients with dyslipidemia.  
_Am J Cardiol_. 2002;89:672-678.
The discovery and development of modern medicines from plants is not usually a straightforward process. Scientists believe that the correct way to discover a new remedy is by knowing the mechanism of action of a plant compound and matching it with the biochemical basis of the disease process. However, it is not usually like that. Careful observation by itself can yield dividends. For example, the antihypertensive action of reserpine was found when psychiatric patients, being treated with Rauvolfia serpentina, had their blood pressure measured as a routine. Academic biochemical research led to the discovery of lidocaine.1

Certainly no one could have predicted that calcium channel blockers would be discovered by way of a somewhat neglected compound found in the opium poppy, but that is exactly what happened with verapamil.

**THE OPIUM POPPY**

Opium is produced by incising the unripe seed capsule of the opium poppy, *Papaver somniferum* L., and drying the milky juice or latex that runs out (Figure 1). The name comes from the Greek words for juice, sap of trees "οίνος," and poppy juice "οπλων," which was Latinized to opium. The Sumerians in southern Mesopotamia cultivated opium and wrote about it as the “joy plant” in 3400 BC. It was used medicinally in Egypt in 1500 BC, also in ancient Greece and Rome, and was introduced into China by Arabian traders. An account of how to get opium by slitting the capsule was written in 50 BC by Scribonius Largus, physician to Emperor Claudius.

One can only guess at the probably dangerous trial and error that led to its discovery as an analgesic and narcotic drug. Opium contains 25 different alkaloids, which are separated into two classes. The important phenanthrene group has 10% morphine, 0.5% codeine, and 0.2% thebaine. The benzylisoquinoline group has 1.0% papaverine, 6.0% narcotine, and 0.3% narceine. The concentrations are given as percentages of purified opium. The latter group has no analgesic or narcotic effects and is not addictive. We are concerned here solely with papaverine.

**PAPaverINE**

Pharmacological studies showed that papaverine (Figure 2) is a relaxant of smooth muscle especially when the muscle is in spasm, but that it does not paralyze the muscle cell that still responds to stimulation. It acts on the muscles of the bronchi, gastrointestinal tract, ureters, biliary system, and arteries. On the isolated heart it depresses atrioventricular conduction and suppresses ventricular premature beats.

In anesthetized dogs with coronary artery ligation it decreases the threshold for ventricular fibrillation and a study in conscious dogs showed that it enhances the coronary blood flow.

In clinical medicine it was used, though with only slight benefit, in children with pyloric stenosis, and a trial done
in 1940 was said to show that it reduced the mortality of pulmonary embolism from 82% to 13%. It was used in systemic arterial embolism, the action being by increase of collateral flow, but Dr Paul D White of Boston reported in 1944 that it had little effect in angina pectoris or in hypertension.

**WIDER USE OF PAPAVERINE**

It was J. Pal in Germany in 1913 who helped put papaverine on the wider therapeutic map. He found that it lowered intestinal tone without interfering with peristalsis and went on to advise its use in gastric and intestinal spasms, in colics and in spastic constipation. We are reminded by the historian Christopher Lee not to judge past events by the standards of the present day, so although “gastric and intestinal spasms” seem to be vague entities, this was still an era of imprecise diagnosis. However, one can easily understand that there was a large market for this type of medicine, notably for constipation, which was then considered a cause of systemic illness. Indeed, the London surgeon W. Arbuthnot Lane was doing colectomy and other operations on the colon in 1909 for “chronic intestinal stasis” in order to treat “auto intoxication”. He was parodied by George Bernard Shaw in *The Doctor’s Dilemma* as the surgeon who operated on the mythical nuciform sac to cure “chronic blood poisoning.”

**PAPAVERINE AND ITS ANALOGS**

Papaverine was isolated in 1848 and its synthesis in 1927 paved the way for the preparation of analogs, aiming for better tolerance and greater specificity of action. Two analogs were synthesized by Merck and Company in Darmstadt and the Chinoin Company in Budapest: Eupaverin and Ethaverine. Walter Sneader comments that they were widely prescribed as antispasmodics in the 1930s, even though they were inferior in this respect to the atropine analogs then in use. The other firm that became interested in this line of enquiry was Knoll AG in Germany, and it was their chemist, Dr Ferdinand Dengel, who developed verapamil.

**VERAPAMIL IS SYNTHESIZED**

Ferdinand Dengel studied chemistry in Munich, Marburg, and also in Frankfurt where he was an assistant to Professor Wagner-Jauregg. He then joined Knoll and went to Vienna where he worked with Professor Ernst Spath. It was in Vienna that he started work on papaverine analogs at Knoll’s request, which he continued in 1938 in Knoll’s own department. After a delay due to the war, his first compound was the spasmolytic Barbonin, but already he was much more interested in finding a cardioactive substance using the homoveratryl test as the guideline. In May 1959, after years of work, he synthesized 75 grams of a viscous oily base labelled D365 (D for Dengel). It was patented on April 28, 1961, with the chemical name of iproveratril hydrochloride and then given the generic name of verapamil (Figure 3).

**THE PHARMACOLOGY OF VERAPAMIL**

Dengel gave a watery solution of his compound to the Pharmacology Department of Knoll where Professor Hans Haas and Dr Gunther Hartfelder found in animals that it had an impressive action in dilating the coronary arteries, but unlike other vasodilators it had negative inotropic and chronotropic effects. In 1964, a Canadian study in animals by Melville et al showed that it impaired atrioventricular conduction.
and that it protected against chloroform/epinephrine-induced ventricular fibrillation. They postulated that it had a “quinidine-like action,” while stating that the actual antiarrhythmic mechanism was not known. But it was still regarded as a β-blocking agent, albeit with unusual features. However, in 1968, after 5 years’ work, Professor Albrecht Fleckenstein of Freiburg showed that the negative inotropic effect resulted from inhibition of excitation-contraction coupling and that the mechanism involved reduction of the movement of Ca\textsuperscript{2+} into cardiac myocytes. Thus was born the concept of calcium channel blockade, a completely new idea in the pharmacology of cardiac muscle. A full account of calcium antagonists with useful references by J. Desmond Fitzgerald was published in this journal.

**CLINICAL STUDIES OF VERAPAMIL**

In 1961, Dr Dengel, having faith in his compound, tested it on himself before it was given to volunteers and patients. On September 1st, 1963, Knoll launched the drug under the name of Isoptin (an old trademark from 1942) and with the chemical name iproveratril. With the aim of treating angina pectoris, three clinics in Germany started trials of the drug, reporting in 1964 to 1966, and the patients in Munster found it so useful that they returned to the clinic asking for further supplies after the trial had finished.

The first controlled double-blind study of verapamil in angina pectoris was done by Sandler and his colleagues in 1968, and they commented that it was still uncertain whether the mode of action was coronary vasodilatation or via myocardial depression. At a dose of 120 mg three times a day they found that exercise tolerance was improved, trinitrin consumption decreased, and most importantly that it had a significant effect on the amount and duration of ischemic ST-segment depression in the exercise electrocardiogram.

The antiarrhythmic action of verapamil having been shown in animals by Melville et al, it was natural to study this effect clinically. An early paper by Schamroth, Krikler, and Garrett in 1972 reported the results in 181 patients to whom it was given intravenously. It was invariably effective in paroxysmal supraventricular tachycardia, while in atrial fibrillation it slowed the ventricular response and often made it regular, the mechanism for this being uncertain. The drug was useful too in atrial flutter and in the preexcitation syndrome. They wrote, “as a calcium ion antagonist and thus an antagonist of electromechanical coupling, it may belong to a novel class of antiarrhythmic agents.” In vitro work in Oxford by Singh and Vaughan Williams showed that verapamil’s mode of action required that it be placed into the previously unknown Class IV.

A hypotensive effect of verapamil had been noted in two studies of anginal patients and, by 1970, reports of its use in hypertension started to be published. In 1978, Lewis and colleagues in New Zealand did a careful double-blind crossover trial that confirmed its value in hypertension. The response was dose-dependent and well seen with 120 mg three times a day. They emphasized the virtual lack of side effects at all dose levels, although, predictably, this original optimism had later to be somewhat tempered, eg, in particular due to the risk of congestive heart failure in subjects with severe left ventricular dysfunction, or the risk of hypotension.
Following these early studies there have been about 20,000 papers published that refer to verapamil. There are now at least 11 calcium channel blockers on the market and because they differ in their possible sites of action their therapeutic actions are different. There are important differences between verapamil and the dihydropyridine blockers such as amlodipine. Readers of this journal will be well aware of the various compounds available and the indications for their use.

We are taught a further lesson in the history of drug discovery when we learn that the therapeutic scope of verapamil has widened in an unforeseeable way to become the first compound to be effective against multidrug resistance in cancer.

**BOTANY AND HORTICULTURE**

Papaver was the original Latin name for poppy. The poppy family, *Papaveraceae*, which has 23 genera and over 200 species is found in the northern hemisphere, mostly in temperate regions. The species are nearly all herbaceous, though occasionally there are small shrubs. There are four subfamilies, one of which, *Eschscholziadeae*, is found only in North America and contains the California poppy (*Escholzia or Eschscholzia californica*), the state flower of California. The family was named by the distinguished French botanist Antoine de Jussieu who worked at the (still extant) Jardin des Plantes in Paris in the mid-1800s. French cardiologists will know the nearby Metro station Jussieu.

The opium poppy, *Papaver somniferum* L. is a handsome plant, up to one meter high with large grey green pinnately lobed leaves (Figure 4). The unopened flower buds are nodding and the flower color varies from white to violet and red. The nonfleshy fruit is a capsule and when mature the seed is released through pores in the roof of the capsule. The seed is tiny and one plant will release many hundreds. It is an annual. Although it is common in the Middle East and Asia, it actually originated in the western part of the Mediterranean region.

The flowers of the poppy family are usually single and often very beautiful (Figure 5). In my garden I grow the yellow horned poppy *Glaucium flavum*, which is a feature of the nearby shingle beach and also *Argemone mexicana*, the prickly poppy of Mexico, together with the Oriental, Iceland, and California poppies and of course the opium poppy, which seeds itself freely.

The poppy family has uses other than the medicinal ones of morphine, codeine, and papaverine, which occur only in *Papaver somniferum*. Opium poppy seed contains no alkaloids and is used, for its nutty flavor, to sprinkle on cakes and bread. It also yields a culinary oil, olivette, and an artists’ oil. Seeds of the prickly poppy and the yellow horned poppy contain oils that have been used in the manufacture of soap.

One needs a warmer climate than Britain to obtain a good yield of opium. Afghanistan is the source of 80% of the world’s opium and in 2004 it produced 3400 metric tons, which could yield 765 metric tons of heroin (Figure 6). However it is interesting to find that Tasmania with its mild climate on the 41st parallel produces 40% of the world’s legal supply of opiates (Figure 7). It also grows a genetically modified strain containing no opiates, but rich in the alkaloid thebaine, from which a painkiller, oxycodeine, is produced.

I would like warmly to thank my wife Dr Catharine Hollman for the painting of an opium poppy flower. Also I thank Dr Dennis M Krisker for his advice, and the staff of the Rosewell Library, Conquest Hospital, Hastings, for their valued assistance.
REFERENCES

1. Hollman A.
Coca, barley, and the giant reed: the discovery of local anaesthetics and their use in cardiology.

2. Sneader W.

3. Melville KI, Shister HE, Huq S.
Iproveratril: experimental data on coronary dilatation and antiarrhythmic action.
CMAJ. 1964;90:761-770.

4. Fleckenstein A, Doring HJ, Kammermeir H.
Einfluss von Beta-Rezeptorenblockern und verwandten Substanzen auf Erregung, Kontraktion und Energiestoffwechsel der Myokardfaser [Influence of β-receptor blockers and related substances on the stimulation, contraction, and energy metabolism of myocardial cells].
Klin Wochenschr. 1968;46:343-351.

5. Fitzgerald JD.
Calcium antagonists and the importance of pharmacological specificity of action.

Clinical evaluation of verapamil in angina pectoris.

7. Schamroth L, Krikler DM, Garrett C.
Immediate effects of intravenous verapamil in cardiac arrhythmias.

8. Singh BN, Vaughan Williams EN.
A fourth class of anti-dysrhythmic action? Effect of verapamil on ouabain toxicity, on atrial and ventricular intracellular potentials, and on other features of cardiac function.

9. Livesley B, Cattet PF, Campbell RC, Oram S.
Double blind evaluation of verapamil, propranolol and isosorbide dinitrate against a placebo in the treatment of angina pectoris.

10. Lewis GRJ, Morley KD, Lewis BM, Bones PJ.
The treatment of hypertension with verapamil.
Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients

Antithrombotic Trialists’ Collaboration

BMJ. 2002;324:71-86

Many trials have been carried out with aspirin and other antiplatelet agents, demonstrating efficacy in the reduction of serious vascular events in a wide variety of patients at high risk of such events. Indeed, the authors of this paper had previously published a meta-analysis of such studies in 1994. This was repeated in 2002, in order to address some of the questions that remained unanswered. For example, it was unclear when antiplatelet agents should be initiated after ischemic stroke, and questions remained about the possible benefits from aspirin therapy in patients with chronic atrial fibrillation, stable angina, and peripheral arterial disease (PAD).

Among 448 possibly suitable trials, 166 were excluded for a variety of reasons. The included studies were of patients at high risk of a vascular event, randomized to aspirin or placebo in 197 of the trials, and aspirin versus another antiplatelet regimen in the remaining 90 trials. Randomized patients had a likely annual incidence of an event of >3% due to a predisposing condition or previous event.

The numbers of included patients allowed the authors of this analysis to subcategorize results according to the condition that the trial was investigating, such as acute myocardial infarction (MI) or acute stroke, and also by the event prevented, such as death, MI, or stroke. The death rate combining all studies was 13.2% in the control group and 10.7% in the aspirin group, though this was measured over a variety of time periods according to design of individual trials. This reduction was highly significant, at \( P < 0.0001 \). Benefits of similar magnitude and statistical significance were seen in trials of aspirin in the treatment of patients with acute myocardial infarction (MI), previous MI, previous stroke, or transient ischemic attack and other vascular events. The relative risk reduction for each was approximately 25%. This was less striking in acute stroke at 11%, though still highly significant \( (P=0.0009) \). In this condition, aspirin was associated with worsening hemorrhagic stroke and hemorrhagic transformation of ischemic stroke, which partially cancelled the benefits of thromboembolic stroke reduction.

A summary of this length cannot hope to mention all the individual analyses in this meta-analysis, since there were 14 categories of disease for which patients were enrolled. However, for each of the main categories—coronary artery disease, PAD, high risk of embolism (atrial fibrillation and valve replacement/surgery), and other high-risk conditions—aspirin demonstrated important and significant reductions in vascular events. The authors suggest that the failure to demonstrate benefit among diabetics is explained by many of the analyses having confidence intervals that were as wide as the magnitude of benefit, thus increasing the likelihood of false negatives findings.

There was no difference in the efficacy at doses from 75 to 150 mg, 160 to 300 mg, and >500 mg, though toxicity was greater at the highest doses. Thus, 75 to 150 mg is recommended except when a rapid treatment effect is required, when a loading dose of 150 to 300 mg may be given.

This study showed that aspirin therapy is effective in preventing vascular events in patients with stable angina and intermittent claudication, and may be given in atrial fibrillation if warfarin is unsuitable. Despite the issues mentioned above, it is beneficial to initiate it promptly in acute stroke. When aspirin cannot be given, clopidogrel was found to be an appropriate alternative.

The National Academy of Sciences opposes human reproductive cloning, but supports therapeutic cloning; France returns to South Africa the remains of the “Hottentot Venus,” aka Saartjie Baartman, born in 1789 and exploited as a circus freak; and a woman injured by an exploding cappuccino machine in a Starbucks café is awarded $3.5 million by a Manhattan jury.
Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies

K. Wilson, N. Gibson, A. Willan, D. Cook

Arch Intern Med. 2000;160:939-944

This paper comprises a meta-analysis of 12 articles addressing the risk after myocardial infarction, and the impact of smoking cessation. Smoking remains the leading cause of preventable death in the United States, with 400,000 people dying per year from smoking-related causes. Individuals with ischemic heart disease who continue to smoke have been shown to be at particularly high risk, due to the widespread effects of the cigarettes’ constituents, including adverse effects on coronary blood flow, myocardial oxygen demand, and the risk of thrombosis.

A thorough review of the medical literature databases was conducted as well as searching through the citations of relevant articles, which revealed 12 useful papers that were included in this meta-analysis. In these studies, nearly 12,000 patients had been enrolled between 1949 and 1988 from across Europe and the USA. Smoking status was assessed at 1 to 12 months, and in two studies ongoing assessments were performed. Cessation rates of 29% to 74% were recorded during follow up of 2 to 10 years.

Mortality rates ranged from 4% to 37% among the ex-smokers, and 8% to 54% among the ongoing smokers, with relative risk reductions of 15% to 61%. The combined odds ratio for death among the ex-smokers was 0.54 (95% confidence interval [CI], 0.46-0.62). This suggested that with an estimated mortality rate among ongoing smokers of 20%, the number needing to quit smoking in order to save one life is 13! Comparing all the papers, there were surprisingly few differences in methodology that might have been expected to skew results. All except one study required self-certification of smoking status, which is a potential weakness, though one that would be likely to reduce the magnitude of benefit seen. The benefits of smoking cessation were observed in all subgroups, and were independent of gender, country of study, timing of study (prior to or after 1980), and length of follow up.

It is striking to observe that the odds ratio of 0.54 in favor of smoking cessation compares extremely favorably with meta-analyses of other interventions in the treatment of myocardial infarction (MI). For thrombolysis, the equivalent figure is 0.75 (95% CI, 0.71-0.79), for aspirin it is 0.77 (95% CI, 0.70-0.84), and for β-blockers, it is 0.88 (95% CI, 0.80-0.98). These analyses only included randomized controlled trials, which have a higher validity than cohort studies, which made up all of the papers in this meta-analysis.

The limitations of this analysis include the inherent weaknesses of cohort studies. In such studies, it is possible for unequal distribution of confounding variables to occur, though in the studies that controlled for infarct size and age as possible confounders, this was not found to be the case. Although individuals who were motivated to stop smoking might have made better use of medical services, and thus received more effective post-MI management, such an effect would have caused a change in the odds ratios after 1980, after which many of the currently accepted therapies were more widely introduced. Although publication bias is a common concern in performing meta-analyses, the authors calculated that it would require 241 null result studies to cause this analysis to produce a nonsignificant result.

The authors conclude by stating that this provides compelling evidence for the benefits of smoking cessation post-MI, and that studies should now be directed at interventions to increase the success of smoking cessation.
Bulpitt, in this paper, discusses strategies for secondary prevention of established and stable coronary artery disease in the elderly and the very elderly (age 80 years or more). The author points out that there is little evidence from randomized controlled trials to guide our decisions in the very elderly, as most major studies have few, if any, elderly participants. The author argues that it is inappropriate to simply extrapolate findings from younger age groups to the elderly since they vary in many ways from younger patients. For example, physiology changes with age, and this cohort is mainly female. Patients may have dementia or impaired renal function, they may be on multiple-drug therapies for comorbidities, and they may have a perception of how, and how long, they wish to live, which is at variance with that of younger patients.

There is good evidence that, in the elderly, smoking cessation reduces mortality. Being overweight is a good prognostic sign in the very elderly and advice to lose weight should possibly be restricted to the obese. Exercise should be encouraged. It is the author’s personal opinion that dietary change is difficult to institute in the very elderly. Little is known about alcohol consumption in the very elderly except that they tend to drink less than the young. However, moderate alcohol consumption is likely to confer some cardiac survival benefits.

Antiplatelet agents should be prescribed. There is evidence that in the elderly (>65 years) aspirin causes an absolute reduction of 4.5% in vascular events. It is also possible that the incidence of both dementia and gastrointestinal cancer is reduced. However, there is a 3% absolute increase in gastric bleeding, a 40% relative increase in hemorrhagic stroke, and a higher incidence of anemia.

β-Blockers result in a 6% reduction in total mortality at age 65-75, but are underprescribed in this age group. Concerns regarding postural hypotension, bradycardia, bronchospasm, peripheral vascular disease, and masking of hypoglycemic events warrant careful monitoring of these drugs in this age group. There are no trials of β-blockers in subjects over the age of 80 years. Angiotensin-converting enzyme (ACE) inhibition gives an absolute risk reduction of 3.3% in subjects over the age of 70. All patients should be prescribed these, with the only limiting factors being hypotension and postural hypotension. Lowering blood pressure is directly related to a reduced incidence in vascular events, at least until around 79 years. Recent trials in the very elderly (>80 years) showed that active treatment of hypertension significantly reduces stroke, major coronary events, and heart failure. However, there was also a tendency toward increased cardiovascular deaths and total mortality. For every stroke avoided, there was one excess nonstroke death. Trials on the subject are currently being undertaken.

The benefit of statins in reducing coronary events is well established. Below age 80, the benefit of treatment greatly outweighs any disadvantage. Above this age, however, although coronary events are reduced (19%), no evidence of a reduction in stroke incidence has been shown. In addition, cancer incidence increased with pravastatin by 25%.

The author suggests that the minimum secondary prevention for the very elderly should be the institution of cardiac rehabilitation and antismoking advice, together with the prescription of antiplatelet and ACE-inhibitor treatment.

The New England Journal of Medicine reports that if obesity in children continues, their life expectancy will be cut by 2 to 5 years; Pope Benedict XVI beatifies Charles de Foucauld (1858-1916) soldier, explorer, Trappist monk, and hermit in the Algerian Sahara; and Steve Fossett completes the first solo, nonstop round-the-world flight when his plane GlobalFlyer lands in Kansas.
Beta blockade during and after myocardial infarction: an overview of the randomized trials

S. Yusuf, R. Peto, J. Lewis, R. Collins, P. Sleight

Prog Cardiovasc Dis. 1985;27:335-371

At the time this paper was published, 65 trials had enrolled 50,000 patients to determine the effects of β-blockers in the treatment of myocardial infarction (MI). The effect of early IV administration was assessed separately to early oral and chronic oral administration, both in individual studies and also by these authors. This is explained by the variation in type of complication by time post-MI. In the early hours after MI, it is thought that 20% to 50% of patients die due to ventricular fibrillation (VF). In those surviving this early hazard, the short- and long-term determinant of morbidity and mortality is the volume of infarcted myocardium. It is known that factors that increase oxygen demand, such as tachycardia, heighten the severity of injury, and there are also indirect influences on oxygen demand. Increased adrenergic activity increases circulating free fatty acids, which may lead to arrhythmias and also increase myocardial oxygen consumption.

β-Blockers reduce cardiac work by lowering heart rate and blood pressure, hence reducing myocardial oxygen demand. Furthermore, lower effective adrenergic drive may result in favorable redistribution of coronary blood flow, thus protecting viable myocardium.

In the studies of early administration of β-blockers, it had been expected that a limitation of infarct size would be seen, but the long duration (>12 hours) to effective blockade with oral agents eclipsed the period of peak risk and meant that no mortality benefit was seen. Early IV administration was associated with a reduction in peak cardiac enzyme level by 20%, and improved R-wave preservation on the ECG, both of which indicate a reduction in infarct size. A reduction in arrhythmias was seen and though the studies did not reveal a mortality benefit, they were not powered to do so.

This analysis demonstrated for the first time that long-term β-blockade showed a reduction in mortality from 10.1% to 8.0% (P<0.0001). Because of their relatively small size, only 2 of 16 trials individually demonstrated a mortality benefit, and similarly, it was not possible to identify the likely magnitude of benefit for specific subgroups. By combining studies, highly significant reductions in reinfarction (25%) and in sudden death (30%) were seen. Comparable benefits were seen across a range of different β-blockers except those with intrinsic sympathomimetic activity, which offered much lower protection.

Surprisingly, the level of side effects was only slightly higher among patients given β-blockers than placebo, though no statistical analysis of this could be performed. Concerns had been raised that β-blockade might cause excess rates of bradycardia, heart block, significant hypotension, or cardiogenic shock, though surprisingly no significant increase was observed. However, most trials excluded those with overt heart failure or at highest risk of these complications.

This study was one of the early meta-analyses, and the authors provide a highly informative discussion of the principles and assumptions used in performing such an exercise. While such analyses are now widely accepted and frequently used, this excellent summary remains highly relevant today.

In conclusion, early IV β-blockade seemed to limit infarct size, and might reduce mortality. The authors indicated that the forthcoming International Study on Infarct Survival (ISIS) was likely to clarify this question. Long-term administration certainly reduces mortality by approximately 20%, though the benefit is uncertain beyond 12 months.

1985

Mikhail S. Gorbachev replaces Konstantin Chernenko as Soviet leader;
Milos Forman’s film of the life of Mozart, “Amadeus,” wins the best film category at the 57th Academy Awards;
and India files suits against Union Carbide over the Bhopal disaster.
Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients

S. Yusuf, P. Sleight, J. Pogue, J. Bosch, R. Davies, G. Dagenais; the Heart Outcomes Prevention Evaluation Study Investigators


**H**OPE, (Heart Outcomes Prevention Evaluation) established evidence of benefit for angiotensin-converting-enzyme (ACE) inhibitors for a new set of indications. It was previously known that ACE inhibitors improved the outcome in patients with left ventricular dysfunction, irrespective of the presence of symptomatic heart failure.

In HOPE, the ACE inhibitor ramipril was given to patients with preserved left ventricular function, but who were at high risk of cardiac and vascular events. Inclusion criteria were an age of at least 55 years, and a history of coronary artery disease, stroke, peripheral artery disease, or diabetes, with at least one cardiovascular risk factor (hypertension, elevated total cholesterol, depressed high-density lipoprotein cholesterol, cigarette smoking, or microalbuminuria). Patients known to have heart failure or with an ejection fraction (EF) below 40% were excluded. Although echocardiography was not routinely performed, a subgroup of 496 patients was investigated more intensively, in which the incidence of low EF was only 2.6%.

Compliance with the therapy was good, with 87.4% of patients assigned to the ramipril arm taking it at 1 year, and 78.8% at the final follow up visit, at 5 years. The target dose was 10 mg per day, and the proportions taking this dose at 1 and 5 years were 82.9% and 75%, respectively. The most common reason for discontinuing therapy in the ramipril group was cough (7.3% versus 1.8% in the control group). A slight drop in the blood pressure was observed in both the ramipril and the placebo groups, but this was slightly more marked in the ramipril group (mean reduction 3/2 mm Hg).

The primary outcome measure of the study was the composite outcome of myocardial infarction, stroke, or death from cardiovascular causes. A significant difference between the two groups was observed from 2 years and this was maintained until the end of the study, by which time 14.0% of the ramipril group had accrued one of the primary endpoints, compared with 17.8% of the control group (P<0.001, relative risk [RR], 0.78, 95% confidence interval [CI], 0.70-0.86). There were significant reductions in some of the secondary outcome measures, including revascularization and diabetes complications, though surprisingly not hospitalization due to either unstable angina or heart failure. Other benefits seen included a reduction in the risk of heart failure, cardiac arrest, worsening angina, and a new diagnosis of diabetes. These benefits were observed in those taking a variety of other agents known to be beneficial, including aspirin, β-blockers, and lipid-lowering agents.

The authors explain that the benefits seen were probably only partly due to blood pressure-lowering effects. Other mechanisms include direct effects on the heart or vasculature, including antagonism of the direct effects of angiotensin II, which causes vasoconstriction, vascular smooth muscle cell proliferation, and plaque rupture. In addition, ramipril improves vascular endothelial function, reduces left ventricular hypertrophy, and enhances fibrinolysis. The reduction in the incidence of diabetes and diabetes complications is explained by a possible increase in insulin sensitivity, reduced insulin clearance, and mirrors findings from the Captopril Prevention Project and in subsequent trials of ACE-inhibitors and angiotensin receptor blockers (ARBs).

This study increased the range of indications for ACE inhibitors and predicts that treating 1000 patients for 4 years would prevent 150 events in 70 patients. The simplicity of the trial, its applicability to everyday practice, and the magnitude of benefit have had a profound impact on prescribing habits.
It is well established that angiotensin-converting enzyme (ACE) inhibition effectively reduces mortality and morbidity among patients with heart failure, left ventricular dysfunction, after myocardial infarction (MI), with hypertension, and among other high-risk patients. The beneficial effects of ACE inhibition appear to be due to many factors. In addition to lowering blood pressure, ACE inhibitors possess direct cardiovascular protective effects through angiotensin II reduction and increased bradykinin availability. Consequently, ACE inhibition may result in reduced neointimal formation, improved endothelial function, plaque stabilization, and fibrinolysis. This multifactorial antiatherosclerotic profile of ACE inhibition suggests that its application might be extended to all patients with established coronary heart disease (CHD) and should not be restricted to patients with impaired left ventricular function, heart failure, or those at high risk of atherosclerotic events.

This study aimed to assess the ability of the ACE inhibitor perindopril to reduce cardiovascular death, MI, and cardiac arrest in patients with stable CHD and without heart failure or substantial hypertension. No patient had clinical evidence of heart failure, but all had evidence of CHD; previous MI, angiographic evidence of coronary artery disease, coronary revascularization or a positive stress test only. A total of 12,218 patients were randomized to the drug or to placebo. Mean follow-up was 4.2 years. There was good compliance with the study medication and only 7% needed to reduce the perindopril dose from the full 8 mg to 4 mg (cough, hypotension, or abnormal creatinine). Most patients were taking concomitant medication at randomization, 92% of the patients were taking platelet inhibitors, 62% β-blockers, 58% lipid-lowering therapy.

The primary end point was a composite of cardiovascular death, nonfatal MI, and cardiac arrest with successful resuscitation. Secondary end points were the composite of total mortality, nonfatal MI, hospital admission for unstable angina, and cardiac arrest with successful resuscitation, also cardiovascular mortality and nonfatal MI, as well as the individual components of these secondary outcomes and revascularization (coronary artery bypass grafting or percutaneous coronary intervention), stroke and admission for heart failure.

The primary end point occurred in 488 patients (8%) in the treatment compared with 603 (10%) in the placebo group (P = 0.0003). The benefit began to appear at 1 year (relative risk reduction 10%, P = 0.35) and gradually increased throughout the trial. The authors estimate that 50 patients need to be treated for a period of 4 years to prevent 1 major cardiovascular event.

The benefits reported for perindopril were in addition to other preventative measures, including aspirin, β-blockers, and lipid-lowering, and were consistent for all patients and subgroups. The benefits were greater than might be expected for the observed reduction in blood pressure (mean 5/2 mm Hg), and the effect was similar in those with treated hypertension and those without hypertension. This implies that the specific antiatherosclerotic effects of ACE inhibition should not be neglected.

The authors conclude that the results provide strong support for consideration of perindopril in all patients with CHD irrespective of other preventative treatments, cardiac function, or risk factors.

Palestinian Prime Minister Mahmoud Abbas steps down, claiming both Ariel Sharon and Yasser Arafat have undermined his position; Sweden votes against adopting Europe’s single currency in a referendum; and the New England Journal of Medicine reports that injection of intestinal hormone peptide YY (PYY) reduces appetite in both fat and thin individuals.
Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)

Scandinavian Simvastatin Survival Study Group

Lancet. 1994;344:1383-1389

Prior to 1994, when this study was published, there had been several trials of cholesterol-lowering interventions in primary and secondary prevention. Various methods and medications have been tried to lower lipid levels, including partial ileal bypass surgery. However, no clinical trial had convincingly showed that lowering of cholesterol prolongs life. Physicians were being conservative and cholesterol-lowering agents were not standard therapy in secondary prevention of coronary heart disease. The Scandinavian Simvastatin Survival Study (4S) study showed that long-term treatment with simvastatin improved survival in CHD patients. Simvastatin is a hydroxyl-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor.

4S was a large study involving 94 clinical centers throughout Scandinavia, recruiting a total of 4444 patients. Patients were aged 37 to 70 years with a history of angina or previous myocardial infarction (MI) and a total cholesterol level of 5.5 to 8.0 mmol/L. Patients were excluded if they had a history of complicated MI with significant myocardial dysfunction or required drug therapy for heart failure. The design was double blind and patients were randomly assigned to simvastatin 20 mg or placebo. Dietary advice was given to all. At 6 months, patients with cholesterol levels still out of range (>5.2) were given an increased dose of 40 mg (37%). Median follow up was 5.4 years.

Changes in baseline total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol and serum triglycerides were -25%, -35%, +8%, and -10%, respectively in the simvastatin group. The corresponding values in the placebo group were +1%, +1%, +1%, and +7%.

The main end point, total mortality, was significantly reduced by simvastatin, with a relative risk of 0.7. Looking purely at coronary deaths, the risk reduction was even greater at 42% (relative risk 0.58) in the simvastatin group. Secondary end points also showed benefit from simvastatin. The relative risk of major coronary events (nonfatal MI, silent MI, resuscitated cardiac arrest) was 0.66. Tertiary end points: any coronary event, any atherosclerotic event (including cerebrovascular accident), percutaneous transluminal coronary angiography, coronary artery bypass grafting, and hospital admissions for non-MI coronary heart disease, were also reduced in the simvastatin group.

In addition, the study showed that simvastatin was safe. A single case of rhabdomyolysis occurred in a woman taking 20 mg once daily. Creatine kinase increased to 20 times normal in 1 placebo and 6 simvastatin patients, but none experienced muscle pain or weakness, the levels fell again without stopping any therapy. Aspartate aminotransferase (AST) increased similarly in both groups, alanine aminotransferase (ALT) also rose in both groups, but slightly more in the active group. Prior to this trial there had been some concerns about a potential increase in violence and cancer with lipid lowering. Although these end points were measured, no such effect occurred.

The authors speculate as to how cholesterol lowering may mediate the observed effect—coronary lesions may stabilize as their lipid core shrinks or at least does not further enlarge, there is thus a drop in risk of plaque rupture, hence in intramural hemorrhage and intraluminal thrombosis, which in turn may cause coronary events. Stabilization of coronary lesions is the most likely mechanism underlying the improved survival observed in the trial. The authors continue and suggest that if simvastatin by lowering LDL cholesterol can lower mortality, then LDL cholesterol should be an important factor in the pathogenesis of CHD.

1994

South Korea lifts the ban on business and economic links with the North;
King Hussein of Jordan makes his first official visit to Israel; and Microsoft founder Bill Gates pays a record $30.8 million at Christie’s New York for an original treatise written by Leonardo da Vinci
The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels


CARE (Cholesterol And Recurrent Events) was designed to answer the question of how to treat patients following myocardial infarction (MI), in whom cholesterol levels were within the accepted normal range. In this paper, Sacks et al report that the relationship between cholesterol and coronary events is stronger at higher levels of cholesterol. Aggressive treatment of cholesterol had been shown by angiography to reduce progression of coronary stenoses, or even cause regression. These benefits were shown to relate to the pretreatment cholesterol level. However, the majority of patients with MI have cholesterol levels close to the population average and it remained unclear how to treat this group.

Four thousand patients were enrolled into this study at 3 to 20 months following MI. To be included, the total cholesterol level had to be <6.2 mmol/L (240 mg/dL), with low-density lipoprotein (LDL) cholesterol 3.0-4.5 mmol/L (115-174 mg/dL). Patients were randomized to receive either pravastatin 40 mg or placebo. Regular monitoring of cholesterol was performed, and if LDL levels rose above 4.5 mmol/L, patients were given advice, cholestyramine, or referred to their primary physician for further treatment. There was a significant reduction in cholesterol levels in the pravastatin group, with the mean LDL falling by 32% from 3.6 to 2.5 mmol/L, which was 28% lower than in the placebo group. The primary end point of fatal coronary heart disease or MI was 24% lower in the pravastatin group at 10.2% versus 13.2% in the control group ($P=0.003$). In addition, while the incidence of nonfatal MI was 6.5% and 8.3%, respectively ($P=0.02$), the lower incidence of fatal MI (1.2% and 1.8%, respectively) was of only borderline significance ($P=0.07$). There were significant reductions in the rates of coronary artery bypass surgery, coronary angioplasty, and stroke, and a borderline fall in rates of hospitalization for unstable angina. However, there was a non-significant 9% reduction in the overall mortality.

These benefits were seen at all ages and were independent of left ventricular ejection fraction. For all patients except a cohort with the lowest starting lipid levels (LDL <3.2 mmol/L), benefits were seen, and the number in this lowest group was small. Consistent with previous studies, the benefits seen were more pronounced at higher starting lipid levels. There was no excess of side effects or abnormal biochemical parameters in the treatment group. A slightly higher rate of breast cancer was observed in the treatment group, though this was felt to be due a lower than expected rate in the control group, and thus due to chance.

Thus this study proved that cholesterol lowering in patients with average levels of cholesterol following MI lowered coronary death rates and nonfatal MI, and it implied that the average cholesterol level was higher than ideal. Furthermore, the reduction in stroke that had been found in post-hoc analyses of previous studies was confirmed as a predetermined end point in this study. Although 4S produced greater benefits, the authors suggest that this was more due to a higher starting cholesterol level rather than simvastatin being more effective than pravastatin. The authors calculate that prescribing pravastatin as in this study to 1000 patients would prevent 150 cardiac events, including 37 fatal or nonfatal MIs.
The correlation between low-density lipoprotein (LDL) cholesterol and ischemic heart disease (IHD) risk had been observed for some years prior to the inception of this trial. Although there was still some controversy over the relationship, the authors explain that it is essentially linear, with no definite lower threshold in Western populations below which risk tailed off. Studies of lipid-lowering medications had shown that in high-risk patients a reduction in LDL was associated with a fall in mortality and morbidity. No such data were available in those without a prior diagnosis of IHD, but considered to be at high risk by virtue of other vascular disease or diabetes. Nor were data available for the elderly, females, and those with lower LDL levels, but with multiple risk factors. Approximately 20,500 patients were entered into this study, which compared simvastatin 40 mg with placebo over 5 years, although 11,000 more were excluded following a rigorous “run-in” phase designed to exclude those with poor compliance, a failure to respond to the medication, or with side effects. Those included were of both sexes, aged 40 to 80, and had a total cholesterol of at least 3.5 mmol/L. Patients were required to have a previous history of coronary or non-coronary vascular disease, diabetes, or if male over 65 years, hypertension. In addition, a study of antioxidants (vitamins C and E, and β-carotene) was performed in the same population, though this failed to demonstrate any benefits.

Due to noncompliance in the statin group, and the prescription of open-label statins to those in the placebo group, the authors felt that observed differences represented only 67% of the real difference between the groups. A mean reduction in LDL of 1.0 mmol/L was seen. The total mortality was 12.9% in the treatment group and 14.7% in the controls, \( P=0.0003 \). A similarly significant reduction in coronary mortality was seen (5.7% vs 6.9%). In addition, highly significant reductions were seen in the incidence of first nonfatal myocardial infarction, first nonfatal stroke, as well as the rates of angioplasty and coronary artery bypass surgery. These were summarized by the major vascular events rate being 19.8% and 25.2%, respectively, \( P<0.0001 \).

These benefits were observed at all ages, including 75 to 80 years at time of randomization, and in both sexes, as well as all other major subgroups (LDL <2.5 mmol/L, diabetes and no vascular events, cerebrovascular disease, and peripheral arterial disease). In addition, despite the widespread use of other effective therapies including aspirin, β-blockers and angiotensin-converting enzyme inhibitors, these benefits were maintained.

Concerns had previously been expressed that very low LDL levels might be associated with an excess morbidity due to other conditions. These were specifically sought, and no excess of cancer, abnormal liver function tests, cognitive decline, or respiratory impairment was observed. The rate of significantly abnormal creatine kinase levels was very low, and although slightly higher in the statin group (7 vs 1 cases), this was of borderline significance.

The authors conclude that prescribing should reflect future risk rather than be determined by the absolute LDL level. This is determined by the coexistent risk factors and pre-existing disease. Such treatment not only reduces the risk of coronary events, but other vascular events, and indeed these benefits may be up to 30% greater than revealed by the nature of the “intention-to-treat” analysis used.
Exercise training has been historically accepted as being of benefit following myocardial infarction (MI). Indeed, Heberden observed in 1772 that one of his patients with presumed ischemic heart disease was “nearly cured” after 6 months of daily wood sawing for half an hour. Although exercise rehabilitation programs were widely available at the time this paper was written, the only trials conducted failed to show any statistical benefit due to being underpowered.

In this paper, studies of exercise alone, and exercise combined with advice on risk factor reduction, were reviewed. Due to the heterogeneous nature of the trials, and indeed of the exercise programs, each study is considered alone, and in combination with the others. The end points considered were total mortality, cardiovascular mortality, sudden death, and fatal and nonfatal MI. Although 36 trials were found in the literature, 14 were excluded due either to the nature of randomization or short duration of follow-up.

In total, these studies had enrolled approximately 4500 patients, among whom there had been 502 deaths. There were 412 cardiovascular deaths, and 202 sudden deaths. Of the 701 MIs that occurred, 312 were fatal. Individually, only two studies demonstrated a significant reduction in death, though overall, the relative risk of death at 1 year was 0.77 (95% confidence interval [CI], 0.59-1.01), at 2 years this risk was 0.74 (0.59-0.92) and 3 years 0.80 (0.66-0.96). The mortality was slightly lower in those who received risk factor advice as well as exercise compared with exercise alone, though this difference was not significant. Death due to MI or other cardiovascular causes demonstrated a similar pattern to that described above. Rates of nonfatal MI were slightly higher among those receiving rehabilitation, which implies either that exercise increases the risk of MI or, more likely, that it increases the likelihood of survival following MI. In addition, there was a significant reduction in sudden death among exercisers in the first year with an odds ratio of 0.63 (0.41-0.97) though, conversely, in the latter years, there was a trend to an increase in death in this group. The highest rate of sudden death following MI is usually observed during the first year, which may account for the benefit at this time. The authors explain that the analysis is based on time from randomization, as data were not consistently available on time from MI, which may thus diminish the observed level of benefit derived from exercise.

By the nature of the studies reviewed, there are limitations to the conclusions that may be drawn from this analysis. The authors explain that although additional advice on diet and smoking cessation tended to be beneficial, this was not statistically significant. Some end point data were missing and it is not possible to predict whether this leads to an under- or overestimate of benefit. The authors state that it is unlikely that there was a bias due to failure to publish “negative” trials. Few women were included, and most subjects were under 65 years of age, and thus conclusions are limited to men under this age.

The benefits observed probably occur because exercise lowers heart rate and blood pressure, and is associated with lower circulating norepinephrine levels. Weight loss, improved metabolic efficiency of muscle, and increased coronary collateral formation may also contribute.

In conclusion, exercise programs, possibly combined with advice relating to other secondary preventative measures, are of benefit following MI.

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1989

The space probe Voyager 2 makes its closest approach to Neptune, discovering new moons and a planetary ring system;
Tadeusz Mazowiecki is elected first noncommunist president of Poland;
and Roger Kingdom (USA) sets the 110-m hurdle record (12.92s) in Zurich
### Secondary Prevention

#### Bibliography of One Hundred Key Papers

selected by Eva Lonn, MD, MSc, FRCPC, FACC; Jasmine Grewal, MD, FRCPC

*Division of Cardiology - McMaster University - Hamilton Health Sciences, General Site - Hamilton Ontario - CANADA (e-mail: lonnen@mcmaster.ca)*

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<td>Albert MA, Danielson E, Rifai N, Ridker PM; PRINCE Investigators</td>
<td>Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. <em>JAMA</em>. 2001;286:64-70.</td>
</tr>
</tbody>
</table>


Clarke R, Lewington S, Youngman L, Sherliker P, Peto R, Collins R.

Underestimation of the importance of blood pressure and cholesterol for coronary heart disease mortality in old age.
*Eur Heart J.* 2002;23:290-293.

Colhoun HM, Betteridge DJ, Darrington PN, et al; CARDS Investigators.

Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial.

Criqui MH, Denenberg JO.

The generalized nature of atherosclerosis: how peripheral arterial disease may predict adverse events from coronary artery disease.


Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol.

Daly CA, Fox KM, Remme ME, Ferrari R, Simoons ML.

The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: results from the PERSUADE substudy.
*Eur Heart J.* 2001;26:1369-1378.

Dargie HJ.

Effect of carvedilol on outcome after myocardial infarction in patients with left ventricular dysfunction: the CAPRICORN randomised trial.


European guidelines on cardiovascular disease prevention in clinical practice.

de Lemos JA, Blazing MA, Wiviott SD, et al, for the A to Z Investigators.

Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial.


Mediterranean alpha-linolenic acid-rich-diet in secondary prevention of heart disease.

Dzau VJ.

The cardiovascular continuum and renin-angiotensin-aldosterone system blockade.
*J Hypertens.* 2005;23(suppl 1):S9-S17.

Dzau VJ, Berstien K, Celermajer D, et al.

Pathophysiologic and therapeutic importance of tissue ACE: a consensus report.

EUROASPIRE I and II Group.

Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. European Action on Secondary Prevention by Intervention to Reduce Events.

EUROPA Investigators.

Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study).
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title and Details</th>
</tr>
</thead>
</table>
HOPE Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE study. 


Jha P, Flather M, Lonn E, Farkouh M, Yusuf S. The antioxidant vitamins (E, C and beta-carotene) and cardiovascular disease: a critical summary of epidemiological and clinical trial data. 

Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). 


JAMA. 2002;288:351-357.


Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. 
BMJ. 2002;324:1570-1576.

BMJ. 2003;326:1427.

Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. 
BMJ. 2003;326:1423.

Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? 


Lerman A, Zeiher AM. Endothelial function: cardiac events. 


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<tr>
<th>Author(s)</th>
<th>Title and Source</th>
</tr>
</thead>
</table>

Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group.


Sacks FM, Pfeffer MA, Moye LA, et al. 

The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels.


Scandinavian Simvastatin Survival Study Group. 

Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S).


Schwartz GG, Olsson AG, Ezekowitz MD, et al. 

Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial.


Simes RJ, Marschner IC, Hunt D, et al. 

Relationship between lipid levels and clinical outcomes in the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels.


Smith S Jr, Blair SN, Bonow RO, et al. 


Snow V, Barry P, Fihn SD, et al; American College of Physicians; American College of Cardiology Chronic Angina Panel. 

Primary care management of chronic stable angina and asymptomatic suspected or known coronary artery disease: a clinical practice guideline from the American College of Physicians.


SOLVD Investigators. 

Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions.


Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum J. 

Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity.


Task Force on Beta-Blockers of the European Society of Cardiology. 

Expert consensus document on beta-blockers.


Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE In tolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials.


Torp-Pedersen C, Kober L; TRACE Study Group. 

Trandolapril Cardiac Evaluation. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction.

<table>
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<th>Author(s)</th>
<th>Title and Details</th>
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