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Scientific Update™

Prevention of Coronary Artery Disease: Myth or Reality?

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Over the past four decades there has been an important reduction in mortality from coronary artery disease in both men and women. Current evidence suggests that environmental factors play a greater role than genetics in the wide variation of the prevalence and incidence of coronary artery disease among countries. Reductions in cardiovascular mortality appear to be largely the result of changes in lifestyle (principally a reduction in fat intake and smoking). Despite strong evidence supporting the benefits of blood-pressure control in reducing cardiovascular disease, adequate long-term 24-hour control remains poor even in the 50% of the population recognized as hypertensive. Control of hyperlipidemia is also limited to a small proportion of patients at high risk of cardiovascular morbidity, despite excellent evidence supporting its benefits in patients at risk. Reducing blood pressure, cholesterol, and smoking – rather than reducing generalized progression of the disease – are likely to have a greater role in stabilizing coronary atherosclerotic plaque, thereby preventing plaque rupture and fissure, which lead to myocardial infarction. The increased recognition of patients at risk and their treatment using agents that provide both adequate 24-hour protection and additional anti-atherosclerotic and antioxidant benefits could make further progress in reducing the impact of Canada's number-one killer.

Introduction

Ischemic heart disease remains the number-one cause of mortality in Canada. Although the disease is more prevalent in the elderly, it is an important cause of death and premature morbidity for men in their most productive years. The death rate and need for interventions in women increase approximately 10 years later than in men, soon catching up to similar rates by age 70. Over the past 30 years there has been an important reduction in age-corrected mortality from coronary artery disease (CAD) in most western countries. It remains unclear whether this decrease in death rates is entirely due to primary prevention of atherosclerosis or is partly a consequence of secondary prevention in patients who have advanced atherosclerosis.

Risk factors or genetics?

CAD is predominantly a disease of the industrialized world. However, death rates from CAD range widely from very low levels in Japan and France to high rates in the United Kingdom, especially in Scotland and Northern Ireland. Are these wide variations due to genetics or environment? Assuming that differences in CAD death rates are not due to variations in the classification of sudden death, studies of the incidence of risk factors as well as the healthcare systems in individual countries might provide an insight into the relative importance of environment and genetics.

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Table 1: Acute myocardial infarction, hypertension, smoking, and elevated total cholesterol levels in Japanese men resident in Japan, Hawaii, and California (Ni-Hon-San Study).[1]

	Japan	Hawaii	California
Acute MI (per 1,000)	7.3	13.2	31.4
Hypertension (%)	9.3	1.4	4.6
Smokers (%)	74.0	43.0	36.0
Average total cholesterol (mmol/dL)	4.7	5.6	5.9

The study of populations who move from an area with a low prevalence of CAD to one where the disease is common suggests that environment and risk factors play an important role. Japanese men who move to Hawaii and California have a marked increase in their rate of acute myocardial infarction (MI) despite a reduction in both hypertensive heart disease and smoking[1] (refer to table 1). The increase in total cholesterol is sufficient to explain the increased incidence of CAD in a similar genetic population, and it suggests the pivotal role of lipids in causing the disease.

Observations in countries such as those in the Eastern Bloc – where the incidence of ischemic heart disease mortality has increased at a time when it has fallen in most other countries – relate the increase in CAD mortality to an increase in income, which is associated with increased consumption of fatty foods and cigarette smoking. Such observations can never be used as evidence for causative association, but they certainly support the hypothesis that environment is more important than genes.

Significant reductions in CAD death rates have been achieved in the United Kingdom despite the very high prevalence of the disease. Some of this benefit might have resulted from a population strategy aimed at reducing fat intake to less than 35% of the diet and saturated fat to less than 11%, decreasing blood pressure and cigarette smoking, and increasing the consumption of fresh fruits and vegetables. Systolic blood pressure continues to be reduced despite an increase in both obesity and alcohol consumption, each associated with hypertension. However, despite less smoking in adults over 16 years old, there is a special concern about the increased cigarette consumption in young people (especially females) aged 11-15 years. If this trend continues, there will likely be a resurgence of smoking-induced vascular disease in 30-40 years. Support for the theory that prolonged smoking promotes vascular disease is seen in the increasing incidence of abdominal aortic aneurysm, an incidence that parallels the increase in cigarette smoking 30-40 years ago. If this theory is correct, we should now observe a leveling off of the incidence of aortic aneurysm, paralleling the peaking of cigarette consumption 30 years ago.

Multiple studies have proven the benefits of risk-factor control in patients at high risk of death from CAD. Controlling hypertension reduces mortality from cerebrovascular accident by 40% and CAD by 20%, yet less than 60% of the UK population is aware that it has hypertension. Forty-five percent of these patients take antihypertensives, and 26% of the hypertensive patients are adequately controlled by UK standards (systolic BP <160 mm Hg, diastolic BP <95 mm Hg). Despite the proven value of lipid lowering in both patients with CAD (e.g., 4S[2] and CARE[3]) and patients at high risk of disease (e.g., WOSCOP[4]), the use of lipid-lowering agents in the UK is confined to 1.2% of all hyperlipidemic patients who might benefit.

This failure to control hyperlipidemia has mainly resulted from the perception that 25% of the population would need treatment if safe lipid levels, as currently defined by secondary prevention studies, were to be attained. As this is clearly unreasonable, there has been apathy in selecting higher-risk patients who will benefit. One approach is to risk-stratify patients according to age, blood pressure, smoking habit, and cholesterol level. After attempting to change modifiable risk factors such as smoking, diet, blood pressure, and weight, the decision to use cholesterol-lowering medication would be based on the new risk assessment. Although cholesterol-lowering medications in high-risk patients have proven benefit but are underutilized, primary population measures such as stopping children from

smoking and improving diet and blood pressure will have a greater impact on more people and will improve the health of future generations.

Risk factors and progression of CAD

Acute MI usually results from coronary artery thrombosis occurring at the site of a deep rupture of an atherosclerotic plaque; in more than 60% of cases, this is not associated with significant coronary artery stenosis. Early lesions of atherosclerosis are common in young and apparently healthy men and are not visible on coronary angiograms. By the time minor angiographic lesions are apparent, severe atherosclerosis is present; in fact, an angiographically visible coronary irregularity is more likely to cause an acute infarction than is significant coronary artery stenosis.

Little et al[5] studied the relationship between angiographic appearance of the site of vessel occlusion before and after acute infarction in 42 patients. At the follow-up angiogram, 29 patients had a newly occluded artery; in 19 of the 29, the occluded artery had less than 50% stenosis, and 28 of the 29 patients had an artery with less than 70% stenosis. Twenty-five of the 29 patients had at least one site of significant coronary artery stenosis on their baseline angiograms; however, only in 10 of the 29 patients did the site of the occlusion correspond to the most severely stenosed vessel. In the patients with no significant stenosis at the location of the subsequent obstruction, vessel wall irregularity was visible on the pre-infarct angiogram. Thus it has become clear that there is a poor correlation between the severity of the coronary lesion and its propensity to occlude.

Plaque rupture is most likely to occur at the sites of plaques that have a large lipid-rich core and a thin fibrous cap with a vigorous inflammatory cell infiltrate. Certain other features of CAD make stenoses more likely to progress: e.g., location of stenoses in the right coronary artery, in vessels greater than 2 mm diameter, in the proximal or middle segments of the vessel, at sites of low shear stress, in focal rather than diffuse disease, and in complex rather than smooth lesions.

Progression of atherosclerosis and hypertension

The link between hypertension, its treatment, and the progression of atherosclerosis was evaluated in a SHEP (Systolic Hypertension in the Elderly Program) substudy.[6] Prior to this study, there had been considerable concern that undue lowering of diastolic arterial pressure would result in an increase in cardiovascular mortality: the J-curve phenomenon. The SHEP trial[7] showed the beneficial effect of treating elderly patients with isolated systolic hypertension, producing a reduction of four-year cardiovascular event rates. The substudy[6] found a relationship between the cardiovascular event rate and the presence of carotid or lower-limb atherosclerosis: no atherosclerosis in 4.8% of subjects, subclinical atherosclerosis in 16.7%, clinically apparent atherosclerosis in 24%.

However, carotid and peripheral vascular atherosclerosis were not distributed evenly over the blood-pressure range. Although the presence of atherosclerosis was related to elevations in systolic BP, smoking, and abnormal lipids, the best predictor was a diastolic blood pressure less than 75 mm Hg. Studies of the ratio of intimal-to-medial thickness also showed that this indicator of atherosclerosis correlated best with high systolic and low diastolic pressures.

Is the wide pulse pressure the cause or the effect of atherosclerosis? The SHEP substudy[6] suggested that systolic hypertension was a cause of atherosclerosis. It showed that progression of carotid artery atherosclerosis was reduced in treated patients and that the odds of progression were 4.3 times greater in the placebo group than in patients on treatment. Furthermore, all patients who showed evidence of regression of atherosclerosis were in the treatment group.

The benefits of treating patients with systolic hypertension were observed in patients who had normal diastolic pressures prior to treatment. Reducing systolic pressures was associated with a fall of average diastolic pressures to 75-65 mm Hg – an effect that, according to the J-curve theory, should be associated with an increase in cardiovascular mortality. SHEP showed that the lower cardiovascular complication rate associated with the reduction of systolic pressure occurred despite the lower diastolic pressures, a benefit that might have resulted from a reduction of vessel wall stress and plaque rupture. The SHEP studies suggest that controlling systolic blood pressure not only limits the progression of atherosclerosis but also stabilizes the vulnerable atherosclerotic plaque, thereby reducing the chance of plaque rupture and acute arterial thrombosis.

Stabilization of vulnerable plaque is also the likely mechanism for the benefits observed with cholesterol reduction in patients at risk of cardiac events. The important

reductions in event rates observed in the FATS study[8] were inadequately explained by the small changes in coronary stenoses, and they were more likely a consequence of stabilization of vulnerable coronary plaque. Traditional risk factors are associated with the progression of atherosclerosis; however, the rapid benefits observed within one to two years of blood-pressure reduction, smoking cessation, and cholesterol lowering are more likely to be the result of plaque stabilization rather than reduced atherosclerosis. Despite the excellent evidence supporting the benefits of treatment, only a small proportion of patients at risk have adequate control of risk factors.

Treating hypertension to prevent CAD

Conventional control of blood pressure is often based upon a single measurement, assumed to be representative of arterial pressure during the patient's day, yet ambulatory 24-hour recordings of blood pressure clearly show wide variations throughout day and night. The concept of 24-hour blood-pressure load on the cardiovascular system as a determinant of outcome is supported by the observation that 24-hour blood-pressure measurement is a much better prognostic indicator than an isolated recording. In addition, the incidence of target-organ damage – such as left ventricular hypertrophy, impaired left ventricular function, microalbuminuria, and hypertensive retinopathy – correlates best with both the average 24-hour blood pressure and the variability of blood pressure over a 24-hour period rather than with the isolated blood-pressure measurement. It is therefore likely that reducing target-organ damage as well as atherosclerosis progression and its complications (i.e., stroke and MI) requires full 24-hour protection from excessive arterial pressures. Adequate control should reduce overnight blood pressures, lessen the waking-rising surge, and prevent an increase in any 24-hour variability of pressure.

It is unfortunate that only a small proportion of the hypertensive population is either recognized or adequately treated. A common aphorism is that approximately 50% of hypertensives are recognized; of these, only 50% receive treatment; and of the treated hypertensives, fewer than half have adequate control – that is, only 12.5% of the total hypertensive population receives adequate blood-pressure treatment. In the UK, 23% of men and 28% of women treated for hypertension achieve adequate control as defined by an isolated pressure measurement of <160 mm Hg systolic and <95 mm Hg diastolic; however, such target pressures are probably not adequate to make an optimal impact on cardiovascular mortality.

Using 24-hour blood-pressure recordings, Mancia et al[9] showed that the majority of treated hypertensive patients had only a small daytime reduction in pressure and that no antihypertensive activity was detectable during the early-morning period, which is the time of maximal cardiovascular complications. Many hypertensive patients take medications that produce a cyclical fall in blood pressure over 24 hours with a good maximal reduction in pressure yet an inadequate duration of control; this produces a false sense of adequate blood-pressure control if the blood pressure is measured during the medication's maximal effect. Many agents often considered to provide adequate 24-hour blood pressure control – especially the "longer-acting" angiotensin-converting-enzyme inhibitors – might produce better average blood-pressure reduction with less blood-pressure variability if administered twice daily.

Adequate blood-pressure control over many years must be our goal if hypertensive cardiovascular disease is to be controlled. The Framingham Heart Study supports the need for long-term control.[10] This observational study suggests that a 10-20 year period of treatment reduces cardiovascular mortality by 54% in men and 53% in women while reducing all-cause mortality by 28%. In contrast, an average 16% reduction of cardiovascular mortality was observed in several randomized treatment studies of only 5 years duration.

To prevent CAD and other hypertensive end-organ damage requires 24-hour control of blood pressure over a prolonged period. The ideal medication should be administered once daily, and it should produce a good profile of blood-pressure lowering throughout the 24 hours and beyond, to give some leeway in the time that the patient takes the next dose of medication.

Antihypertensives, oxidative stress, and CAD

Oxidative stress plays an important role in the development of atherosclerosis. Dietary intake of antioxidants,

particularly vitamin E, is associated with a reduced incidence of heart disease. Yet with the exception of the controversial CHAOS study, controlled studies of dietary supplements of vitamin E have been largely unsuccessful in reducing adverse cardiovascular outcomes.

Endothelial-cell membrane damage from free-radical generation is considered central to the pathogenesis of atherosclerosis. There is experimental evidence that antioxidants, such as the E-vitamin tocopherol, reduce the lipid peroxidation of cellular membranes that results from excessive superoxide free radicals. With its hydrophobic chain, tocopherol can enter the lipid bilayer, donate an electron, and inactivate the free radical. Antioxidants such as vitamin C are then necessary to restore the effectiveness of the tocopherol.

Studies in an isolated myocardial cell model have demonstrated the antioxidant properties of several antihypertensive agents. The beta-adrenergic antagonist propranolol has antioxidant properties that are independent of its beta-adrenergic blocking properties because both the d and l isomers have equal antioxidant effect. Propranolol has a hydrophobic moiety that results in the majority of the drug entering the membrane lipid bilayers, and only a small fraction is attached to beta receptors.

In an isolated rat-heart reperfusion model of superoxide and hydroxyl free-radical generation, administering the enzyme superoxide dismutase before reperfusion limits free-radical formation and subsequent injury. In the same model, the recently introduced vasodilating beta-adrenergic blocker carvedilol also limits oxidative-induced injury with a potency similar to that observed with vitamin E. Calcium-channel blocking agents (particularly the dihydropyridine-based nifedipine, nicardipine, and amlodipine, which have important hydrophobic areas on the molecule) have more powerful antioxidant properties than non-dihydropyridine calcium-channel blockers or the most effective anti-peroxidant beta-blocker propranolol.[11]

Endothelial dysfunction plays an important role in both progression and development of the complications of atherosclerosis. Oxidized low-density lipoprotein (LDL) is considered to be a prime mediator of the chain of reactions interfering with the proliferative, anticoagulant, antiplatelet, and vasoreactive roles of the endothelial cell. Recent studies from catheter laboratories have shown that reducing LDL with an HMG-CoA reductase inhibitor improves endothelial-dependent vasodilation.[12] However, the combination of the lipid-lowering agent and the powerful antioxidant probucol resulted in a marked increase in endothelially mediated relaxation of the artery, supporting the hypothesis that oxidized LDL plays an important role in endothelial dysfunction.

Endothelial cells in culture are damaged by the addition of exogenous free radicals, and they rapidly lose their endogenous antioxidant glutathione. Calcium-channel blockers, particularly nisoldipine and amlodipine, can be shown to restore the viability of endothelial cells and their ability to proliferate.[13] X-ray diffraction studies show the location of the amlodipine molecule within the lipid bilayer, able to donate electrons and to protect the membrane lipids from damaging oxidation. Many current antihypertensive agents have additional antioxidant properties that could play a role in limiting progression of atherosclerosis. Only randomized trials comparing equivalent methods of blood-pressure control will demonstrate their clinical benefit.

Conclusion

CAD remains the most important cause of mortality and morbidity in the industrialized world despite an important reduction in death rates from MI. Population studies and controlled trials show the importance of blood-pressure and cholesterol control in reducing mortality from CAD. However, despite the abundance of good evidence, only a small proportion of the population at risk is identified, and an even smaller number receives adequate treatment.

Blood-pressure control must protect the vasculature throughout the day and night and especially in the early morning, the time of greatest risk of all cardiovascular mortality. In patients with isolated systolic hypertension, control of systolic blood pressure should be the aim – with less concern about the effects of reducing diastolic pressures to "subnormal" levels – as cardiovascular mortality and the progression of atherosclerosis both decrease when systolic pressure is reduced. The optimal antihypertensive agent should have a good profile of blood-pressure lowering throughout the 24 hours and

should also have additional properties to limit atherosclerosis. Perhaps the antioxidant properties of dihydropyridine calcium-channel blocking agents will play a role in the prevention of CAD in hypertensive patients; however, only controlled trials will demonstrate their value.

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