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Scientific Update™

New Perspectives in the Treatment of Cardiovascular Disease

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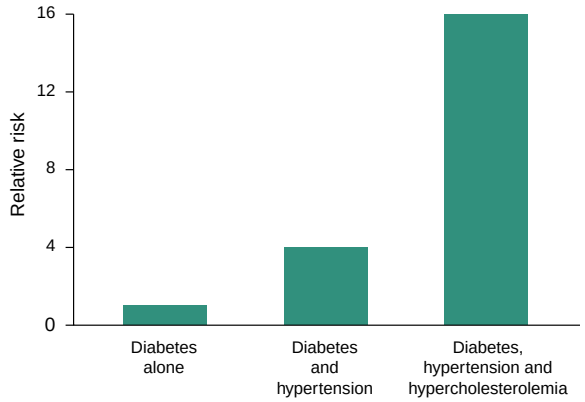
Medical therapy and risk factor modification continue to provide the backbone of management strategies for patients with cardiovascular disease or for those at higher than average risk for developing the disease. This issue covers a number of therapeutic areas which were discussed at the recent international symposium. From primary prevention with lipid therapy, aspirin prophylaxis or control of hypertension in the elderly to treatment of stable angina and modulation of endothelial dysfunction – these management strategies constitute an important consideration in our daily delivery of healthcare to the broad cross-section of patients.

The role of lipid-lowering therapy

Cardiovascular disease (CVD) remains the leading cause of death in North America. By the age of 60, 1 of every 5 men and 7 women will develop coronary artery disease (CAD). One key risk factor for the development of CAD is serum cholesterol. A clear, linear relationship has been established between progressive increases in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) and deaths due to CAD.

While elevated serum cholesterol is a key risk factor in the development of CAD, it is important to assess and stratify patients not only on the basis of their lipid profile but other risk factors that compound the risk of dying from CAD, including smoking, hypertension, and diabetes mellitus (Fig. 1). Even by totalling the number of risk factors (Table 1), it is possible to stratify patients according to their 10-year risk of CAD (Table 2). Based on these risk categories, the primary-care physician can measure a patient's cholesterol profile and individualize dietary therapy, a prescribed exercise program, and, if necessary, lipid-lowering therapy to attain specific target values/treatment goals (Table 2). Importantly, every 10% reduction in total cholesterol reduces the risk of coronary heart disease (CHD) by 30%.

Figure 1: Relative risk of cardiovascular disease in patients with diabetes and other risk factors



– Adapted from Kannel WB. *Am Heart J* 1987;114:413-9

Despite the early suggestion that fibrates, e.g., clofibrate and gemfibrozil and resins, e.g. colestipol and cholestyramine reduce CHD-related deaths, lipid-lowering trials to date have shown no improvement in overall survival rates, partly due to an apparent increase in non-cardiac mortality, e.g., cancer and violent deaths, among study patients. Similarly, the first generation of lipid-lowering trials found that these

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Table 1: Risk factors for coronary artery disease (CAD)
Age • men ≥ 55 years • women ≥ 55 years, or post-menopausal not on HRT
Family history of premature CAD in first-degree relative (men ≤ 45 years; women ≤ 65 years)
Smoking ≥ 1 cigarette per day
Hypertension • systolic BP ≥ 140 mm Hg • diastolic BP ≥ 90 mm Hg • on antihypertensive medication
TC ≥ 5 mmol/l or HDL-C ≤ 0.9 mmol/l
Diabetes mellitus • random venous plasma glucose ≥ 11.1 mmol/l • fasting venous plasma glucose ≥ 7.8 mmol/l • positive 75-g glucose tolerance test • all criteria met twice
Left ventricular hypertrophy
Obesity
Sedentary lifestyle

agents lower cholesterol only modestly – by about 10%. In more recent trials of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) reductase inhibitors or "statins", the degree of cholesterol lowering is 20% to 30%.

In November 1995, the landmark West of Scotland Prevention Study (WOSCOPS) was published.[1] This trial showed that, compared to placebo, pravastatin, 40 mg daily, reduced the risk of non-fatal MI or death from CHD ($p<0.001$) by 31% in 45- to 64-year-old men with moderate hypercholesterolemia (mean TC: 7 mmol/l) and no history of myocardial infarction (MI) over an average of 4.9 years. The risk of death from any cause was reduced by 22% ($p=0.051$). The impressive reductions with pravastatin were explained by a 20% reduction in TC and 26% reduction in LDL-C.

Based on these results, if physicians treated 1,000 middle-aged men with persistent hypercholesterolemia and no evidence of previous MI with pravastatin for 5 years, they would achieve the following benefits: 20 fewer non-fatal MIs, 7 fewer CHD-related deaths, and 8 fewer revascularization procedures, i.e., coronary artery bypass grafting (CABG) or percutaneous coronary angiography (PTCA).

Results of WOSCOPS and several secondary prevention trials[2-4] suggest that these benefits represent a class effect. Therefore, the choice of which statin to use depends on the relative potency and cost of different agents.

Primary prevention of CHD with Aspirin®

The value of Aspirin® for the primary prevention of myocardial infarction (MI) and coronary death is no longer a subject of speculation. Two large randomized studies in men were reported in the late 1980s: the Physicians Health Study[5,6] in 22,000 male U.S. physicians from 40 to 84 years of age with no history of MI or stroke and a British study[7] of 5,100 healthy male physicians.

The prospective, randomized, double-blind, placebo-controlled Physicians Health Study was stopped prematurely after about 5 years of treatment because the rate of MI had already been significantly reduced by 44% among physicians who were randomized to Aspirin® therapy (325 mg, buffered every other day). However, the number of cardiovascular deaths did not differ between the two groups. Furthermore, the risk of moderate-to-severe or fatal hemorrhagic stroke was higher in Aspirin®-treated physicians.

The smaller British study (500 mg daily of Aspirin® vs. no treatment) reported a 10% reduction in total mortality in the Aspirin®-treated group, but this difference was not statistically significant. No difference was found in the incidence of non-fatal MI or stroke. As in the U.S. study, disabling strokes were somewhat more common among Aspirin®-treated participants.

Table 2: Prevention of CAD by control of risk factors

Risk category	No. of risk factors	10-year risk of CAD	Target values/Treatment goals		
			LDL-C (mmol/l)	TC/HDL-C ratio	TG (mmol/l)
Very high	≥ 4	> 40%	< 2.5	< 4	2
High	3	20-40%	< 3.5	< 5	2
Moderate	2	10-19%	< 4	< 6	2
Low	1	< 10%	< 5	< 7	3

CAD = coronary heart disease TC = total cholesterol LDL-C = low-density lipoprotein cholesterol HDL-C = high-density lipoprotein cholesterol TG = triglycerides

When combined, these two studies suggest an 18% reduction in the combined endpoints of MI, stroke, and death.

The role of Aspirin® in primary prevention among women remains unclear, since both trials were restricted to men. A prospective, non-randomized, cohort study in 87,000 female nurses without previously documented CAD or stroke found an age-adjusted relative risk of 0.68 for a first MI ($p<0.005$) among women who reported taking an average of 1 to 6 Aspirin® tablets per week as compared with those who took no Aspirin®. No significant increase in the incidence of stroke occurred in women who took fewer than 15 Aspirin® per week.[8]

While the role of Aspirin® in secondary prevention, i.e. patients with established CVD, has been unequivocally demonstrated,[9] its role in primary prevention is not clear. Primary-care physicians must weigh the potential benefits of Aspirin® in reducing the incidence of first MI – at least in male patients over 50 years of age – against the potential adverse effects of this treatment. Based on current evidence, encouraging smoking cessation and the reduction of risk factors, e.g. obesity, hypertension, and high TC or LDL-C may prove more beneficial.

The optimal management of stable angina

Current medical therapy for stable angina consists mainly of nitrates, beta-blockers, and calcium channel blockers (CCBs). All have established clinical anti-anginal effects and each class is represented by several different compounds. How these approved drugs are used, either alone or together, varies and depends on the patient's individual symptoms and side effects – and physician preference.

Evaluation of the efficacy of these agents has been limited to small studies that primarily focus on surrogate endpoints, such as symptom relief and exercise test or ambulatory monitoring parameters. Large-scale trials that evaluate the safety and efficacy of these agents in stable angina are lacking, but a new trial will soon confront this issue.

A Coronary Disease Trial Investigating Outcome with Nifedipine GITS (ACTION) is a multinational, multicentre, randomized, double-blind, placebo-controlled trial designed to evaluate the effect of long-acting nifedipine GITS (30-60 mg, once daily) on cardiovascular event-free survival in patients with chronic symptomatic angina who are otherwise optimally treated. The study will randomize at least 6,000 patients over nearly 2 years and follow them for at least 4 to 6 years.

This study will include patients who are: ≥35 years of age; in stable condition for ≥1 month but require oral treatment for symptomatic angina either to prevent or treat anginal attacks; have a left ventricular ejection fraction of ≥40%, as documented by two-dimensional echocardiography; and, have not changed anti-anginal medication or taken CCBs within two weeks of randomization.

Patients must have CAD, as defined by at least one of four criteria: unequivocal MI ≥3 months prior to the start of study medication; coronary revascularization ≥3 months prior to the start of study medication; angiographically documented CAD; positive exercise test or perfusion defect on myocardial perfusion imaging.

The primary criterion for the evaluation of efficacy will be a combined endpoint consisting of the rate of: death; acute MI; emergency coronary angiography for refractory angina; overt heart failure; debilitating stroke; and peripheral revascularization.

The sample size of about 6,000 patients will provide an 80% power (two-sided, $p<0.05$) to detect a 14% relative risk reduction with nifedipine in the primary endpoint (assuming a 6 event rate/100 patients years in the placebo group). The ACTION study will be completed and provide important safety and efficacy information on nifedipine GITS in patients with stable angina by the year 2003.

Endothelial dysfunction: a new intermediate endpoint in cardiovascular medicine

Until recently, cardiovascular endothelium was considered only as a passive barrier between the blood and vessel wall. It is now clear that endothelial cells are metabolically active and play a dynamic role in the regulation of normal vascular biology, repair of arterial wall injury, and pathogenesis of atherosclerosis. The endothelium releases numerous substances that not only affect vascular tone but also exert antithrombotic, anti-inflammatory, and growth inhibitory functions.

One of the most important mediators that is released by the endothelium is nitric oxide (NO). It plays a central role in the prevention of atherosclerosis. Adequate levels of NO prevent platelet adhesion and the release of platelet-derived growth factor, one of the most potent growth-promoting mitogens. NO prevents oxidation of LDL-C by scavenging reactive oxygen substances that oxidize LDL-C particles.

At present, no simple, noninvasive clinical tools enable the routine study of endothelial function. However, one of the best treatments of endothelial dysfunction and its related NO deficiency is aggressive risk-factor modification, i.e., better glycemic control, smoking cessation, hypertension and hyperlipidemia therapy, and, possibly, estrogen replacement therapy in post-menopausal women.

Specific pharmacologic agents that act either indirectly or directly on endothelial function include angiotensin-converting enzyme (ACE) inhibitors, CCBs, nitrates, and antioxidants.

Isolated systolic hypertension in the elderly: Systolic Hypertension in Europe (SYST-EUR) Trial

SYST-EUR is a prospective, double-blind, placebo-controlled, randomized trial of nitrendipine, a dihydropyridine CCB, versus placebo therapy in elderly patients with isolated systolic hypertension. This landmark study was initiated in 1989 and stopped prematurely when preliminary follow-up data showed a striking 42% reduction in the primary endpoint of fatal and non-fatal strokes (p=0.003) in nitrendipine-treated, as compared to placebo-treated, patients.

SYST-EUR enrolled patients in 198 centres in Europe and Israel who were ≥60 years of age (mean 70 years) with a sitting systolic BP of 160-219 mm Hg and a diastolic BP of <95 mm Hg. Patients with persistent hypertension after drug therapy were controlled with the step-wise addition of an ACE inhibitor (enalapril) and diuretic (hydrochlorothiazide).

After a mean follow-up of 2 years, nitrendipine had reduced fatal and non-fatal stroke by 42% (p=0.003), fatal and non-fatal cardiac events by 26% (p=0.03), and cardiovascular mortality by 27% (p=0.07). Based on these results, treatment of 1,000 patients for 5 years with nitrendipine would prevent 29 strokes and 53 major cardiovascular events. Over one year, treatment of 1,000 patients would prevent 4 cardiovascular deaths. This result is comparable to the effects of antihypertensive therapy in two large-scale trials of elderly hypertensive patients: STOP-Hypertension (hydrochlorothiazide plus amiloride or one of three beta-blockers vs. placebo)[10] and the Systolic Hypertension in the Elderly Program (SHEP) (chlorthalidone vs. placebo).[11]

While several case-control studies of elderly hypertensive patients have suggested that the use of CCBs may increase the risk of MI, bleeding, and cancer, SYST-EUR – a large-scale, prospective, randomized, double-blind clinical trial – has demonstrated that a dihydropyridine CCB can significantly reduce the incidence of cardiovascular endpoints (including MI) with no increase in the risk of bleeding and fatal or non-fatal cancer. Stepwise antihypertensive therapy that started with nitrendipine significantly reduced the incidence of stroke and cardiovascular complications in older patients (≥60 years of age) with isolated systolic hypertension.

Conclusion

Recent advances, especially in the area of primary prevention by way of large randomized clinical trials refine our ability to identify appropriate treatment goals and strategies.

Frequently, completion of clinical trials also provides important additions to our therapeutic armamentarium, as for example is the case with the findings of SYST-EUR in the treatment of systolic hypertension in the elderly with nitrendipine.

As we expand our treatment options on one hand, and realize limitations in delivery all of these options to all of the patients on the other hand, we will need to develop treatment categories based on patient's risk, perceived (generalization from the results of clinical trials) benefit/risk ratio and cost-effectiveness. From a practical point of view, assessment of individual risk factors will need to focus on management of the patient as a whole. In the multiple risk factor patient, efficacy of treatment, especially in primary prevention, will need to include the issue of compliance as it relates to drug interactions and the use of multiple medications.

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