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Scientific Update™

How to implement best practice: Addressing the difference between knowing and doing

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Atherosclerosis is the most frequent cause of mortality worldwide. Elevated plasma cholesterol levels, in particular, low-density lipoprotein cholesterol (LDL-C), represent a major and modifiable risk factor for development of coronary heart disease (CHD). We now have strong clinical data indicating that morbidity and mortality can be improved through reduction of LDL-C levels using HMG-CoA reductase inhibitors (statins). Therefore, the importance of assuring that patients adhere to treatment guidelines is increasingly evident. This symposium provided an overview of the current management of patients and how best practice can be incorporated into current treatment regimens with the goal of reducing future cardiovascular morbidity and mortality rates.

What do we aim for in lipid management?

The accumulated epidemiological evidence to date suggests a direct relationship between the incidence of CHD and serum cholesterol levels. This relationship can be further refined by the use of LDL and HDL cholesterol values. Most important is the assessment of the total cardiovascular risk profile, which includes other risk factors.

Independent risk factors for stroke-related death are similar, although the relative strength of these risk factors may vary. Given the strength of current epidemiological data, it is not surprising that the mortality rates reported in various trials can now be accurately predicted[1] (Figure 1). The Cardioview™ model can be used to compare the predicted benefits of risk factor modification before and after the development of symptomatic cardiovascular disease (CVD) (Figure 2).

The Cardioview™ model and others confirm that the impact of cholesterol modification is greatest in patients with other risk factors and it is particularly true with respect to primary prevention. In patients with established CHD, treatment of dyslipidemia can be strongly recommended regardless of the profile of other risk factors.

The following points regarding the benefits of risk factor modification should be considered:

- What is the absolute risk of disease?
- What is the relative level of risk?
- What is the remaining life expectancy of this patient?
- How effective is the therapy?
- Is the patient compliant?

Practical management of the patient at risk

Despite advances in our understanding of CVD, the most significant cause of mortality worldwide continues to be coronary artery disease (CAD), accounting for almost one-

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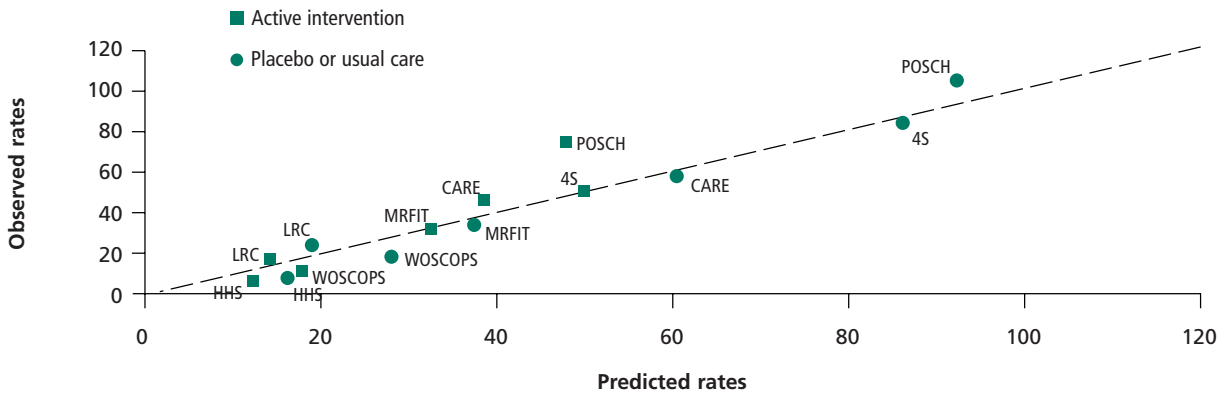
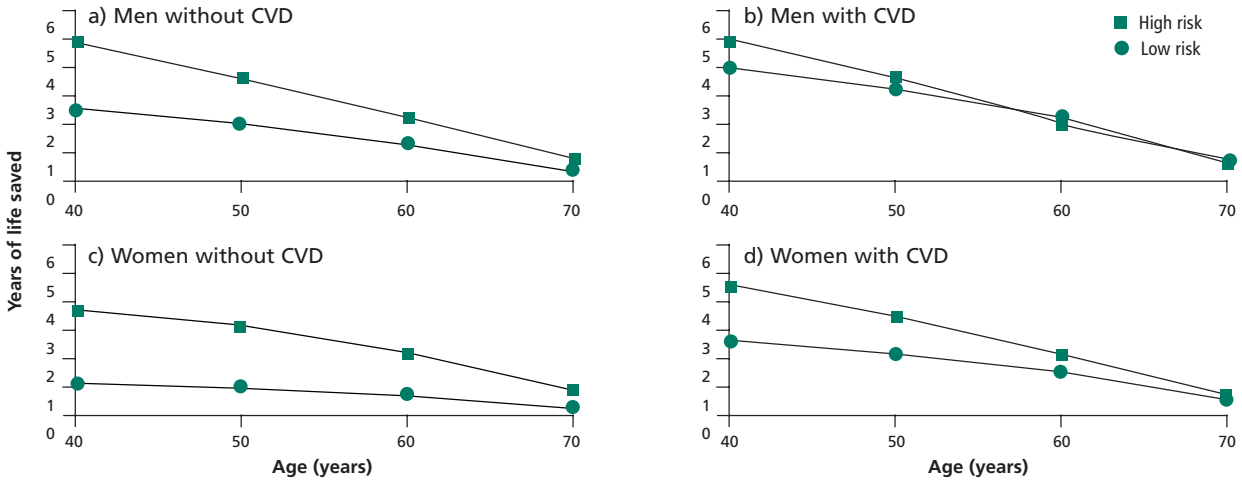
Figure 1: The forecasted rates of death caused by coronary heart disease (CHD) per 1000 using the cardiovascular life expectancy model versus the rates observed in prevention trials.



half of all deaths in developed countries. It is also becoming more prevalent in developing countries.

Recent recommendations for CHD prevention developed by the joint European Societies Task Force (European Society of Cardiology, European Atherosclerosis Society, and the European Society of Hypertension)[1] highlight the multifactorial origin of CHD, focusing on the importance of modifying all major risk factors. Interestingly, these European guidelines have attempted to simplify target levels for "desirable" cholesterol, which should make them easier to remember. For example, the treatment goal for total cholesterol is <5.0 mmol/L; that for LDL-C is <3.0 mmol/L, for all patients (with and without CHD) who require treatment. Thus, the guidelines focus on the importance of treating everybody at risk rather than achieving a very low or strict level of total cholesterol or LDL-C. Other risk modifications highlighted in the guidelines include smoking cessation, and control of hypertension and diabetes, as well as the lowering of plasma cholesterol with lipid-lowering drugs. The use of aspirin, beta-blockers, and ACE inhibitors is recommended for those with established CHD and its complications.

Figure 2: Forecasted years of life saved following lipid level modification in subjects with CVD.



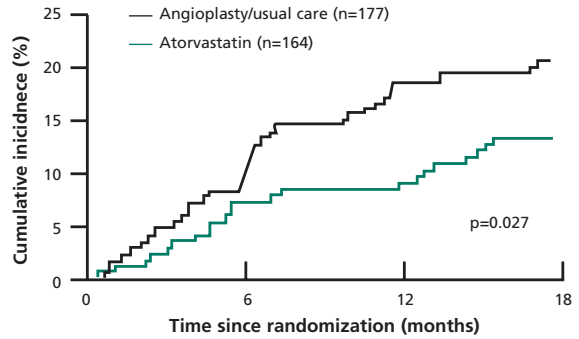
Bridging the gap between recommendations and practice

A recently published EUROASPIRE study[2] demonstrated that among 4,863 patients, 19% continued to smoke, 25% were overweight, 53% had hypertension, 44% had elevated total plasma cholesterol, and 18% were diabetic. Medications included antiplatelet drugs (81%), beta-blockers (54% - 58% in post-MI patients), ACE inhibitors (30% - 38% in post-MI patients); only 32% were taking lipid-lowering drugs. Of the patients receiving blood pressure lowering drugs, 50% had a systolic blood pressure >140 mm Hg and 21% >160 mm Hg. Of those receiving lipid-lowering drugs, 49% had plasma total cholesterol >5.5 mmol/L and 13% had cholesterol >6.5 mmol/L. Thus, despite a high presence of modifiable risk factors and a considerable potential for physicians to reduce CHD morbidity and mortality, there is still a wide-spread failure to achieve the simple goals expressed in these guidelines.

The joint European societies' recommendations suggest that the following processes must be put in place to ensure treatment guidelines are followed:

- integration of care between the hospital and the community,
- extensive screening of families and other blood relatives,
- professional support to assist patients in achieving lifestyle changes,
- pursuit of long-term compliance with proven drug therapies administered at their optimal dosages.

Figure 3: Time to first ischemic event: intent-to-treat analysis



Modern management of the CAD patient: aggressive lipid lowering

CAD is a diffuse disease. Only a minority of coronary artery segments are free of disease either at the time of autopsy or during intravascular ultrasound in patients with CVD. This suggests that metabolic alteration — for example using lipid modification — may be more effective than mechanical intervention, such as revascularization with angioplasty, in reducing subsequent cardiac events. The importance of lipid modification in patients with established disease or in those at risk has already been demonstrated in a number of important trials.[3-7]

A comparison of aggressive lipid lowering therapy vs angioplasty in stable CAD was undertaken in the AVERT study.[8] Of those patients randomized to 18 months of atorvastatin 80 mg/day (which resulted in 46% reduction in the mean serum LDL cholesterol level), 13% had ischemic events — defined as cardiac death, resuscitation after cardiac arrest, MI, CVA, CABG, PTCA, or worsening angina with objective evidence resulting in hospitalization — compared to 21% of patients who underwent PTCA. This represents a 36% relative risk reduction (p=0.048). The observed trend was due to a smaller number of angioplasty procedures, CABG, and hospitalizations for worsening angina. Compared with the patients who were treated with angioplasty and usual care, the patients who received atorvastatin had a significantly longer time to first ischemic event (p=0.03; Figure 3).

Despite the impressive benefit observed in the AVERT study,[8] long-term, large clinical trials have not yet demonstrated reduction in hard endpoints, such as mortality or MI, associated with atorvastatin therapy. In published data, atorvastatin is more effective in reducing total and LDL cholesterol than other HMG-CoA reductase inhibitors when used in currently available formulations.[9-11] In addition to the results of the AVERT Study, future trials with atorvastatin will include:

1) MIRACL, which enrolled approximately 3,000 patients with acute coronary syndromes

2) TNT, which is following 8,600 patients at high risk of recurrent CAD, focusing on the importance of LDL cholesterol reduction below 2.0 mmol/L

3) IDEAL, which is studying approximately 7,600 patients with CAD and will compare 80 mg atorvastatin to 20-40 mg simvastatin and will focus on hard endpoints.

How to implement best practice

The feasibility of achieving the goals presented in the new treatment guidelines is supported by a recently presented study by Barter and colleagues.[12] In this study, the efficacy of atorvastatin 80 mg/day is being compared to that of simvastatin 40 mg/day (supplemented by 4 gm of cholestyramine a day if necessary) in achieving a target plasma cholesterol level of <5.0 mmol/L. The researchers enrolled 1,028 hypercholesterolemic men and women, aged 18-75, who were being treated in a primary care setting. Both atorvastatin and simvastatin were well tolerated with no significant differences in the frequency or severity of side effects. A greater number of patients achieved target LDL-C levels with the starting dose of atorvastatin versus simvastatin. Overall, 83% of atorvastatin-treated patients achieved the target level compared with 66% of simvastatin plus cholestyramine-treated patients. Additional studies have also supported these results, finding that atorvastatin can reduce LDL-C to <2.6 mmol/L in 83% of patients, while 95% of patients reached the NCEP guidelines target. Because of its efficacy, the cost of reaching a target LDL-C is lower with atorvastatin than with other HMG-CoA reductase inhibitors.[13-15]

Conclusion

CAD is multifactorial in nature. Modifications in diet, lifestyle, and other risk factors play an important role in reducing the risk of recurrent cardiac events. Elevated plasma cholesterol levels – in particular, LDL-C – represent a major modifiable risk factor. Thanks to epidemiological and now overwhelming clinical trial evidence, important and achievable treatment guidelines for improving clinical practice have now been established. These guidelines recommend lowering of LDL cholesterol as the primary target of therapy to improve outcome in patients with manifested CAD or in those at risk for cardiac events.

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