EDITORIAL

Cholesterol: A Continuing Controversy

This month in the Hong Kong Practitioner, Drs. Chen and Lo pose the question "The Cholesterol Controversy, Is there one?" Their article leaves little doubt that if there is a controversy, they do not think it is justified. They support the view that hypercholesterolaemia is a major risk factor for ischaemic heart disease, that treatment of hyperlipidaemia produces a regression in atherosclerotic lesions with an associated reduction in deaths from myocardial infarction, and that as a result patients with high blood levels of cholesterol should be identified and treated.

Their position is shared by a large number of people, both physicians and patients. Public concern in the USA, for example, has been reinforced by professional activity, and it is estimated[1] that by 1988 at least 1,000,000 patients were being treated with cholesterol lowering drugs, and the figure is undoubtedly much higher now.

Is such concern, and such a high level of intervention, really justified? I don't believe that it is, and I think there are problems with the evidence regarding the management of hypercholesterolaemia that cannot be overlooked.

In the first place it is much harder than might be supposed to either mount or interpret studies of the association between risk factors such as hypercholesterolaemia and consequent disease. Experimental studies are difficult to apply, and case-control or cohort studies are usually the best that can be managed.

Case-control studies take patients with established disease and retrospectively compare them with a disease-free group for the frequency of exposure to the risk-factor under investigation. Cohort studies follow people before disease is established and compare the different frequencies with which disease develops in people who are and are not exposed to the risk factor under investigation.

The problem is that both these types of study are open to many different forms of bias, with the result that it is difficult to interpret their results . Even if a risk factor is identified, it can be hard to judge whether it actually causes the disease under investigation, is a manifestation of the disease process rather than an antecedent variable, or merely a marker for some other unidentified factor. If it is not actually causal, the risk factor might be predictive of disease, but intervention to modify it would not make a difference.

The identification of risk for coronary heart disease provides a striking example of this dilemma. In 1981 Hopkins and Williams[2] compiled a list if 246 factors associated with coronary heart disease. The list included cold weather, certain fingerprint patterns, noise, a non-supportive boss, being an alcoholic, being a teetotaller, slow beard growth, and increased levels of serum desaturated lecithin!

In the second place, the results of treating hypercholesterolemia, even if it is a central cause of atherosclerosis (an assumption that has recently come under fire[3]), are also debatable.

Grumbach[4] has reviewed four major clinical trials of the drug treatment of hypercholesterolemia. He concludes that even if drug treatment in middle aged men really can prevent death and morbidity, the effect is "modest". He calculates that primary prevention with gemfibrozil or cholestyramine requires treating some 50 men for ten years to prevent one adverse cardiovascular outcome. He also notes that while all the studies he reviewed showed a reduction in cardio-vascular deaths, none showed any benefit in overall mortality because the small reductions in deaths from cardiovascular causes were offset by increases in deaths from other causes.

The failure of trials of cholesterol drugs to lower the overall mortality has concerned other authors. Muldoon and his colleagues[5] reviewed the data from six primary prevention trials of cholesterol reduction, which had involved a total of 24,847 male patients over some five years. While mortality from coronary heart disease was lower in the treated men, the total mortality was not reduced. They concluded that " . . . . the failure of cholesterol lowering to affect overall survival justifies a more cautious appraisal of the probable benefits of reducing cholesterol concentrations in the general population". Of even more concern, a Finnish study[6] of multifactorial primary prevention found that while during the trial itself a reduction of 46% in coronary mortality had been achieved, in the ten years after the trial cardiac deaths and overall mortality were significantly increased in the group that had received the intervention!

Results such as these have caused some authors to question whether in fact there should not be a moratorium on the use of cholesterol lowering drugs. Smith and Pekkanan[1], for example, comment "It is difficult to justify the general use of cholesterol lowering drugs when the data from clinical trials fail to show reductions (and may show increase) in mortality".

Writing in "Circulation", a specialist journal concerned with disease of the cardiovascular system, Hulley and his colleagues[7] also call for a change in direction on health policy with regard to cholesterol. They note three important conclusions that they have drawn from the data so far accumulated in this area.

First, they note that there is an association between low levels of blood cholesterol and non-cardiovascular deaths in men and women, which means that efforts to lower cholesterol in some patients may not be wise.

Second, they find that there is no association between high blood cholesterol and cardiovascular deaths in women and that as a result except in cases at exceptionally high risk, screening and treatment of hypercholesterolaemia in female patients is not justified.

Third, because primary prevention trials have shown an increase in non-cardiovascular deaths of a similar magnitude to the decrease in cardiovascular deaths, they conclude that for primary prevention it seems unwise to treat high blood cholesterol with drugs.

Is there a cholesterol controversy? Unlike Drs. Chen and Lo, I believe there is. I think that despite attempts to produce consensus, considerable confusion continues to exist over clinical policies with regard to the investigation and treatment of hypercholesterolaemia. I find it hard to escape the conclusion that the claims of overall benefit in any but very high risk groups have been overstated, and that the risks of intervention have been ignored for too long. ■

References

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