Selections from current literature: the fight over fat: is pharmacological lipid lowering useful for coronary primary prevention?

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Close on the heels of the discovery of the relationship between serum cholesterol levels and deaths from coronary heart disease (CHD) came enthusiasm for cholesterol lowering as a primary prevention strategy. Whether the theory works in practice has been debated ever since. Hundreds of articles have weighed in on the matter over the last decade. These articles have included primary research, meta-analyses and editorials, and have not lacked for diversity of opinion. In this article I present a half-dozen selections from the literature chosen to illustrate some cautionary points for the primary care physician interpreting the literature.

Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)


One of the earliest, and most influential, of the cholesterol reduction studies is the LRC-CPPT. In this study, 3806 middle-aged men whose cholesterol levels were 265 or greater (the average was 292) were instructed to take six packets a day of either cholestyramine resin or placebo for an average of 7.4 years. Participants were instructed in a moderately low-fat diet as well. A total of 480 000 men were screened to enrol the 3806 trial participants. The report does not give a breakdown of the reasons for exclusion of the 99.2% of men screened who were not admitted. The intervention achieved a 13.9% decrease in cholesterol over 7 years among men who adhered to treatment. The authors report a relative risk reduction of 19% in combined cardiac events [fatal and non-fatal myocardial infarction (MI)]. They conclude that the trial’s results “could and should be extended to other age groups and to women, and . . . to others with more modest elevations of cholesterol levels”.

Comment

Many features of the report reflect the positive spin of the concluding statement. The most obvious of these features is the reporting of relative, rather than absolute, risk reductions. The absolute risk reduction (ARR) for combined coronary events is never given in the report, but is easily calculated from data which are presented. The ARR is 1.6%.

The study population is extremely highly selected, but the report makes no mention of how, or indeed whether, the primary care physician can realistically extend these results to unselected primary care patients as the concluding statement urges.

The authors’ seeming determination to report an impressive positive result extends beyond the choice of relative rather than absolute risk reduction. The statistics are fudged. Though the reduction of combined coronary events is said to be significant at P < 0.05, the tests used are one-tailed. One-tailed tests allow only for the possibility of reduction, not increase, in risk. For a proper analysis, two-tailed tests should be used; if they are, the LRC results fail to reach significance.

The choice of end-point is also optimistic. Though the LRC proposal called for demonstration of reduction in coronary heart disease mortality, the report focuses on combined (fatal and non-fatal) coronary events. The two end-points, fatal and non-fatal, were combined post hoc to achieve significance since, even using the inappropriate one-tailed tests, neither was significant on its own. Total mortality, from all causes, is discussed little in the report, and does not differ between treatment and placebo.

Helsinki Heart Study


Another very influential large trial, the Helsinki Heart Study, randomized 4081 middle-aged men (40–55 years) without clinical or EKG evidence of heart disease to either 600 mg of gemfibrozil twice a day or placebo.
for 5 years. Their non-high-density-lipid (non-HDL) cholesterols had to be at least 200 mg/dl to qualify, and their actual total cholesterols averaged 289. The participants were instructed in a low-fat diet and encouraged both to exercise and to cease smoking. A total of 23,500 men were screened for entry; no details are given regarding non-participants except that 713 were rejected for EKG abnormalities. The intervention achieved an 8% reduction in total and 9% reduction in low-density-lipid (LDL) cholesterols, and reported a 34% reduction in total cardiac end-points. End-points were defined as fatal and non-fatal infarction and sudden death. The authors conclude that gemfibrozil "resulted in a marked reduction in the incidence of coronary disease without evoking any critical adverse events" and that their findings were "conclusive evidence of the role of lipid modification in preventing coronary heart disease".

Comment
In this case, as in the LRC, the ARR is calculable from the report, though never discussed in it. It is 1.4% over 5 years, very similar to that of the LRC results.

The study population is much less extremely selected, but it is still entirely male and inadequate detail is presented to allow generalization to primary care.

The statistics used in the Helsinki report are appropriate two-tailed tests. Only total cardiac end-points reach significance; neither non-fatal MIs nor cardiac deaths do so on their own.

Total mortality is higher in the treatment than the placebo group, though not significantly so. The authors note that the difference is due specifically to an excess of deaths due to violence, and that the same specific finding was observed in other studies, but dismiss it as a chance occurrence.

Holme Meta-Analysis

Holme performed a meta-analysis by a somewhat unusual method, using trials as the unit of analysis, to estimate the treatment effect of cholesterol reduction. Two analyses were done, one for the outcome of CHD and one for total mortality. No search strategy was specified, but included were trials reporting the end-points in question (either or both), and excluded were trials terminated early because of adverse outcomes. Nineteen trials were included, representing blind and unblind studies, single and multiple interventions, diet and drug studies, and both primary and secondary prevention.

By deriving a model relating the logarithm of the odds ratios for the outcomes to the degree of cholesterol lowering, the author concluded that for every 1% reduction in cholesterol a 2.5% reduction in CHD incidence was achieved. He also stated that gains in CHD reduction were mostly offset by losses in other forms of mortality, concluding that at least an 8–9% reduction in cholesterol was necessary for treatment to be of benefit.

The author urges caution in interpretation for two reasons. First, he notes that the results are valid only for reductions from elevated levels and may not apply to normal populations. Second, he mentions, but does not explore, the issue of publication bias favouring trials with positive results.

Canadian Task Force on the Periodic Health Examination Meta-Analysis


The Canadian Task Force (CTF) performed a meta-analysis of trials of lipid lowering, both dietary and pharmacological, for primary prevention of CHD as a step in determining whether to recommend cholesterol screening as part of the periodic health examination. They employed a structured literature review to identify trials for inclusion. Because the intervention under consideration was primary prevention, they included only the six primary prevention trials published as of that time, noting that secondary prevention studies yielded much higher estimates of absolute effect. Their analysis included both dietary and drug intervention studies, finding two of the former (the Los Angeles Veterans Diet Study1 and Minnesotal Coronary Survey2) and four of the latter (the LRC, Helsinki Heart Study, Cooperative clofibrate trial3 and Upjohn cholestipol trial4).

The CTF analysis reports several key points. First, the authors find that lipid lowering for primary
prevention achieves a significant reduction in non-fatal cardiac events. Fatal cardiac events are reduced slightly, but not significantly. They show, in table form, that all six trials (diet as well as drug) experienced increases in death specific to violence, and that this increase is statistically significant. The overall effect is a slight, non-significant increase in all-cause mortality.

The CTF analysis team discuss the issue of study population and maximum achievable benefit in detail. They point out that based on MRFIT's data, lowering cholesterol by 50 mg/dl among men with baseline cholesterols of 300 will hypothetically reduce CHD risk by 50%. However, among men with baseline cholesterols of 200, the same reduction reduces CHD risk by only 8%, and for both women and the elderly the benefits are significantly less still.

The CTF offers the first number needed to treat (NNT) analysis of lipid lowering for primary prevention in our sample of papers. They find that treating 89 hypercholesterolemic middle-aged men for 5 years is necessary to prevent one non-fatal coronary event. They estimate that for average-risk clinical populations, having approximately 25% the CHD event rate of the populations studied, the NNT will be 356.

The conclusion reached by the CTF is that 'there is insufficient evidence for inclusion or exclusion of universal screening for hypercholesterolemia in a periodic health examination'. They recommend considering screening for men aged 30–59 years and drug therapy based on patient preferences if cholesterol remains over 260 after at least 6 months' dietary therapy.

Comment
Read carefully, the CTF report reaches very similar conclusions to those of Holme. Holme's conclusions were, however, very differently presented, leaving the reader with markedly different impressions of the utility of lipid lowering.

The CTF report's recommendations disagreed with those of expert panels in both Canada and the USA. Its lack of the optimism evident in previous publications centres on four issues. The CTF does not dismiss the consistent pattern of increase in violent death seen in clinical trials, but includes it as a side effect in their risk–benefit analysis. The CTF is also circumspect about extrapolating to populations other than those studied, and does so on the basis of clinical-epidemiological calculations of achievable benefit rather than simple blanket assertions. The NNT as an effect estimate provides a rather unvarnished look at how much good the clinician will actually do by pursuing the treatment in question. Finally, the CTF excluded secondary prevention studies, which have very high achievable benefits not applicable in primary prevention.

The CTF report generated considerable indignation in lipid research circles. A frequent argument was that the recommendations were out of date when published, as the trials were based on fibrates and bile acid sequestrants, whereas current therapy was moving toward HMG-CoA reductase inhibitors ('statins'). The controversy, however, ensured an enthusiastic audience for the results of controlled outcomes trials of statins, and that leads us to our next paper.

West of Scotland Coronary Prevention Study (WOSCOPS)

The WOSCOPS randomized 6595 hypercholesterolemic middle-aged men to either 40 mg of pravastatin or placebo daily for an average of 4.9 years. The participants were aged 45–64 years, average cholesterol was 272, and many had other risk factors. Primary end-points were CHD events, both fatal and non-fatal MI, with secondary end-points of angiography and revascularization; 160 000 men were invited for screening, of which 81 161 accepted. Four screening visits were employed, with repeated measurement of lipid profiles to ensure that subjects had genuine stable hyperlipidaemia (all fasting LDLs greater than 155 mg/dl with at least one over 174) while on a lipiddowering diet, and had no major EKG abnormalities or history of MI (though stable angina patients were not excluded).

The degree of cholesterol lowering is somewhat difficult to ascertain; it is reported as being 20% by actual treatment status. Cholesterol by intention to treat is not mentioned but is shown in a graph and appears to be reduced by about 15%. Withdrawal rates were similar between treatment and placebo, and analysis of end-points was by intention to treat. The authors report a 31% relative risk reduction in CHD events, and report the ARR 2.4% over 5 years, as well. There was no increase in non-cardiac mortality in this study.

Comment
Is this it, the definitive evidence that pharmacological lipid lowering is beneficial beyond any doubt, as the accompanying editorial asserts? Using pravastatin, the WOSCOPS trial achieved more than half again the reduction in cholesterol that had been achieved by fibrates or bile salt sequestrants. The consequent ARR in CHD events was half as great again as in the older trials, and was not accompanied by an increase in violent deaths. There is no reason to suppose that other drugs in the same class perform differently than pravastatin.
The NNT derived from these data is only 42 for prevention of a fatal or non-fatal MI. However, the WOSCOPS was, as were the studies cited above, done in a population of middle-aged men with hyperlipidaemia, with a high base rate (7.9% per 5 years for definite, 9.3% for definite + suspected) of CHD events. Applying the extrapolation method of the CTF report, the NNT for lower-risk clinic patients can be estimated at 170 when statin drugs are used.

All these results are predicated upon the patient having genuine hyperlipidaemia, stable on repeated testing. A single elevated cholesterol will not be confirmed on repeated testing in a quarter to a half of cases, and such patients will not derive the benefit demonstrated for patients with true hyperlipidaemia.

Rembold Meta-Analysis


This article is a very recent application of the technique of cumulative meta-analysis, with a strong clinical and clinical-epidemiology orientation. The object of the analysis was to calculate NNTEs for prevention of CHD events (fatal and non-fatal) and for all-cause mortality, for lipid lowering as a primary and a secondary preventative intervention. Literature-search and inclusion criteria were pre-specified, and primary and secondary prevention are separately analysed. The primary prevention analysis included the trials in the Holme and CTF meta-analyses, plus the Pravastatin Multination

and WOSCOPS trials.

The author arrives at two different conclusions, depending on whether the Cooperative trial of clofibrate is included or excluded. When it is included, the NNT for prevention of a CHD event is calculated as 69, and for all-cause mortality 931 (but is not statistically significant). Excluding the Cooperative trial, CHD event prevention NNT is 53 and all-cause mortality is 190. The author is circumspect about extending the results to women and the elderly, suggesting that further research is needed before conclusions can be drawn.

Comment

Although the analysis in this paper is state of the art and done from a practical clinical perspective, the paper addresses generalizability only with regard to women and the elderly. The baseline event rates in the populations studied are not mentioned; in particular, extrapolation of the NNT to middle-aged men with less severe dyslipidaemias is not calculated. Smith has pointed out the importance of considering baseline risk, and calculated that the benefit of lipid lowering accrues only to high-risk populations. Intermediate-risk groups may not be helped, and low-risk ones may actually be harmed. Hence clinical application of this NNT analysis requires the practitioner to be cautious about how closely the patient under consideration resembles those for whom genuine benefit is to be expected.

Opinions are divided about whether to include the Cooperative clofibrate trial in meta-analyses or not. Some authors believe that the increase in total mortality observed in this trial is specific to fibrates, and hence not applicable to current clinical practice.

Summary

The optimistic bias favouring intervention in medicine has long been known, and it may be fair to say that compensating for this characteristic tendency of human judgement is a primary reason for the need for blind trials and evidence-based medicine. Packer has observed that “Physicians frequently decide to prescribe a drug because of the therapeutic gains it might provide (based on pathophysiological theories) rather than the benefits it actually delivers (as demonstrated by the results of controlled clinical trials).” In the present case, sorting out evidence from optimism, what we know from what we wish to be so, is a challenging task for the clinician trying to determine what to recommend to his/her patients in day-to-day practice.

In the case of lipid-lowering therapies, the optimistic preference for positive results is widely evident. Ravskov showed that trials finding a positive result have been cited six times as often as equally sound trials finding no effect. (The LRC alone was cited 612 times in the first 4 years after its publication.) The LRC trial results themselves (interpreted with appropriate statistical tests) were inconclusive and difficult to generalize, but were presented as definitive and generalizable with certainty. Subsequent papers have been more circumspect, but none the less have generally focused on CHD reduction (a positive result) while giving minimal discussion to overall mortality. In this vein, the finding of increase in mortality due to violence has been dismissed outright (e.g. p. 1243 of the Helsinki Study) though it has appeared in fibrate and bile acid sequestrant trials, there is a dose–response relationship, and the same effect is observed in non-human primates. Clinically, increased violence as a side effect may no longer be relevant, as recent analyses suggest that it is specific to fibrates (and to hormones, not used any longer). The currently favoured statin drugs do not so far appear to share this side effect, but it was dismissed by enthusiasts for lipid lowering long before such data existed. Estimates of the effect of lipid lowering are often inflated by including secondary prevention studies, as well as by assertions that 5-year NNTs underestimate the benefits of lipid lowering although
analysis of primary prevention trials indicates that the full benefit of risk reduction is evident within 5 years.16

What is the family doctor to do? Clearly, not all the claims in the literature can be taken at face value, particularly when advanced by content-area experts invested in lipid research. Hence, it seems to fall to the family physician to translate these claims into honest expectations of benefit for the variety of patients we see, with their various levels of risk. Perhaps the best solution is to be found in combining the sound clinical epidemiology approach taken by Rembold with the honest extrapolation of effect according to baseline risk used by the CTF.

We do now have the necessary estimates of NNT for primary prevention to inform our higher-risk patients: an NNT of 53 for CHD events certainly does justify our recommending statin drugs to middle-aged significantly hyperlipidaemic men, especially if they have multiple risk factors. The situation is less clear for lower-risk patients, such as women, the elderly and mildly dyslipidaemic men with no or few other risk factors. Even including the recent data on the statin drugs, the 5-year NNT for prevention of a CHD event in average-risk mildly hyperlipidaemic clinical populations (extrapolated using the CTF method) is 212. What intervention if any the family physician wishes to make, and the patient wishes to take, should be a matter negotiated between them, informed by the family physician’s realistic appraisal of the patient’s likely expected benefit.

References


7 The Pravastatin Multinational Study Group for Cardiac Risk. Patients. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. *Am J Cardiol* 1993; 72: 1031-1037.


9 Holme I. Cholesterol reduction and its impact on coronary artery disease and total mortality. *Am J Cardiol* 1995; 76: 10C-17C.


