EDITORIAL COMMENT

Low and Lowered Cholesterol and Total Mortality*

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The paper by Strandberg et al. (1) in this issue of the Journal confirms that in relatively young, healthy men from higher socioeconomic strata, a (naturally) low total cholesterol (TC) is associated with increased longevity (2); on average, such men will have lower levels of low-density lipoprotein (LDL) cholesterol. Thus, if you are fortunate to have a low TC as a young man, typically a product of a lot of nature and a little nurture, you can expect to do a little better than your peers not so favored.

Can one extrapolate these mortality benefits of naturally low TC in advantaged middle-aged men to middle-aged men of lower socioeconomic status (SES)? Can they be extrapolated to the very low end of the lipid range, or to TC lowered by treatment, or to women or to elderly persons? In each case, the available evidence suggests perhaps not.

Lowest levels. Several prospective population studies have suggested that the mortality benefit associated with lower TC plateaus at levels around 180 mg/dl (3). Indeed, total mortality actually appears to increase somewhat at levels below 180 mg/dl, a finding partially but not completely explained by illness-related reductions in TC and confounding (3). This study does not contradict those observations. The cohort of Finnish men in this study had generally high cholesterol by current standards; only 8% of the population had a TC ≤194 mg/dl (5.0 mmol/l), and when the authors split this group in half, the lower half, with TCs <182 mg/dl (4.7 mmol/l), actually had a slightly higher mortality (27.2%) than the upper half (24.5%). Although the numbers were small and this difference was not significant, the result is concordant with a summary analysis of population studies of both men and women (3).

Lowered by treatment. Lowered TC, either by behavioral intervention or—much more potently—by drug therapy, is a question distinct from naturally low TC. The evidence that pharmacologic therapy of dyslipidemia in higher risk middle-aged men results in a total mortality benefit is extensive and convincing (4). However, from the limited clinical trial evidence available, lowering TC or LDL cholesterol alone produces no independent benefit for clinical events after the ratio of TC to high-density lipoprotein (HDL) cholesterol has been considered (5,6). In only two clinical trials has the issue of the most relevant lipid measure change been addressed, and change in either the TC/HDL ratio (5) or the apolipoprotein (apo) B/apoA1 ratio (6) accounted for all the benefit from drug therapy. After consideration of changes in these ratios, changes in TC and LDL added no predictive value. Conversely, changes in these ratios remained strong predictors even after consideration of changes in TC and LDL. The benefits of statins and other dyslipidemic drugs appear proportional to the degree of improvement in the TC/HDL ratio, and by far the largest reductions in event rates reported to date occurred with combination statin and niacin therapy, with the attendant profound lowering of the TC/HDL ratio (7). Emerging data on the dramatic HDL-increasing effects of cholesterol ester transfer protein inhibitors may prove important for future therapy (8).

Increasingly, evidence shows that the level of TC or LDL alone is a poor guide to whether to begin therapy. A recent trial of high-risk patients showed proportional benefit at every level of baseline TC and LDL (9), making use of such criteria for guiding therapy in high-risk patients (as contrasted with assessing risk) of questionable value.

Women. What about extrapolations to women? To date, there is no evidence for a total mortality benefit in women from dyslipidemia therapy. Two of three trials that have released data on gender-specific total mortality with lipid therapy (6,10) have actually shown increases in the treatment group of 57% and 12%, respectively, whereas the third reported a 1% decrease (11). None of these differences was individually statistically significant. The authors of this editorial have not been successful in obtaining gender-specific mortality data from other trials to further evaluate this question, even from trials completed more than a decade ago. The Cholesterol Treatment Trialists Collaboration is reportedly addressing such questions. However, a PubMed search revealed only two publications to date from this group: both were methods papers, and both were nearly a decade old (12,13). We believe these questions have some urgency. (Since the initial submission of this editorial, a meta-analysis of drug treatment of hyperlipidemia in women has come to a similar conclusion, and the authors have expressed a similar frustration at their inability to obtain gender-specific data from many studies [14]).

SES. What of socioeconomic status? In this study all were “men from the highest social class,” a fact that is extenuated by noting, “in the present study we examined within-group differences, which are probably less sensitive to the selective nature of the cohort.” However, a meta-analysis by Law and Thompson (15) showed that the relation of low cholesterol to cancer on long-term follow-up was not evident in a meta-analysis of high-SES samples but was evident and
significant in meta-analyses of populations of low SES. Indeed, there appeared to be a graded relationship from high-SES populations, to mixed SES, to low SES. This finding cannot be glibly dismissed because there are plausible effect modifiers linked to SES, such as dietary and environmental differences.

**Elderly.** Can we extrapolate the favorable observations concerning low TC in younger persons to older persons? The best evidence is—not really. This article does not address the prognostic implications of low TC once old age is attained. Some evidence suggests that elevated TC in old age is protective (16), and other evidence indicates that in the same person, a TC measured at an older age is much less predictive than a TC measured at a younger age, and a TC measured more distant in time is more predictive than a recent one, even after adjusting each TC measure for the other (17). Only consideration of HDL cholesterol allows much predictive power at middle or older ages (18).

Finally, if TC is a poor predictor in the elderly, or perhaps even a protective factor, should we lower TC in elderly persons? Certainly they are at high cardiovascular risk and, from this standpoint, should benefit from intervention if comparable relative risk reductions obtain and benefits are not undercut by unsuspected hazards. To date only one trial—Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)—has specifically randomized a large number of elderly patients (age 70 to 82 years, mean 75 years) to drug therapy, and all were also at elevated vascular risk for reasons in addition to age (19). The results were not reassuring. The overall benefit for vascular events was a modest 15%, there was no benefit for vascular events in women, there was no benefit for stroke, and there was no benefit for total mortality in both genders combined (readers were not provided gender-specific mortality rates). Moreover, there was a disturbing significant excess of incident cancer in the treatment group, reminding us that elderly persons are at increased risk for cancer as well as cardiovascular disease.

In conclusion, low TC is not uniformly a good thing, and many unanswered questions remain. Appropriate access to relevant data would help clarify some of these questions for researchers and clinicians alike. There is a natural tendency by authors to highlight the most positive findings in their study, particularly where commercial sponsorship is involved. Perhaps medical journals, as a prerequisite for publication, should require investigators and sponsors to make study data accessible after a suitable period to preclude, or at least attenuate, bias in publication.

**REFERENCES**

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