Meta-Analyses of Statin Trials

Clear Benefit for Primary Prevention in the Elderly*

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Many statin meta-analyses have been published, at least 250 according to my just-completed, informal search of PubMed. The endpoint of interest for many of these is incident cancer of a specific type or site (e.g., melanoma, lung, bladder, esophagus, liver, breast, or prostate), but many other diverse conditions have also been reported, including atrial fibrillation, dementia, osteoporosis, and macular degeneration. The broad scope of these studies is a consequence of the widespread use of statins and their multiple biologic effects due to inhibition of the 3-hydroxy-3-methylglutaryl CoA reductase enzyme. Most of these studies have inherent limitations: they use observational datasets of varying quality and not clinical trial data, endpoint definitions are often not uniform, sample sizes may be too small, and publication bias may influence the results.

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The “Rolls Royce” of statin meta-analyses is the Cholesterol Treatment Trialists’ Collaboration (CTTC). Their analysis plan was agreed upon before any of the statin trials were available, and was published in 1995 (1). The Collaboration comprises members of the steering committees of the trials, and they analyze patient level data. The CTTC established that the relationship between low-density lipoprotein cholesterol (LDL-C) reduction and cardiovascular (CV) event reduction is approximately linear, with each mmol/l reduction in LDL-C associated with a 21% reduction in events (2). The implication of this is that profound LDL-C reduction will yield profound CV event reduction.

The CTTC analyses conclusively show that the relative risk reduction from LDL-C lowering with statins is independent of baseline LDL-C, across the range from 3.5 mmol/l and above down to below 2 mmol/l (3). The implication of this is that the decision to treat should depend upon the level of CV risk and not the level of LDL-C. Most recently, the CTTC has reported that relative risk reduction is independent of the level of baseline risk; although subjects at higher risk obtain more absolute risk reduction, significant risk reduction still occurs when the 5-year risk of a major vascular event is 5% to 10%, or even <5% (4).

A clear message from the CTTC reports is that all patient categories enjoy approximately the same relative CV event reduction with statins: primary and secondary prevention; men and women; young and old; and subgroups with diabetes, hypertension, current smokers, and different levels of high-density lipoprotein cholesterol, body mass index, and renal function (2,3).

Nevertheless, some meta-analyses have focused on subgroups of clinical interest, usually where risk is low. For example, in a meta-analysis of 6 trials, including 11,435 women without CV disease published in 2004, no significant benefit was seen with statins for any of the CV endpoints (5). The authors did report benefit among women with established CV disease, and allowed that the lack of benefit for primary prevention in women may have been due to the small number of events. Such caution was wise, because their conclusion was soon reversed. In a meta-analysis of statins for primary prevention in women published 6 years later with larger numbers (6), the relative risk of CV events for statin-treated women was 0.63 (95% confidence interval: 0.49 to 0.82; p < 0.001), with a trend toward a reduction even in total mortality (relative risk: 0.78; 95% confidence interval: 0.53 to 1.15).

When is it essential to have clinical trial data for specific subgroups before treating them? In my opinion the answer is almost never; it is far better to include these subgroups in pivotal trials from the start. But, one could argue that perhaps women, diabetics, or Asians are sufficiently different in important ways from the predominantly male, Caucasian population of statin trials. For the elderly, similar arguments can be made.

At least some evidence suggests that statins might not be effective in older individuals. With increasing age, total cholesterol and LDL-C lose their ability to predict CV events and total mortality (7), and in the very elderly, low cholesterol levels are associated with an increased mortality risk (8). In a large observational study of Medicare patients discharged from the hospital after myocardial infarction (MI), treatment with a statin was associated with reduced mortality at 3 years in patients younger than age 80 years, but not in those age 80 years or older (9).

The consequences of MI and stroke are much more serious for older than younger patients, both for death and long-term disability. The incidences of CV events also increases with increasing age. For these reasons, the elderly without evidence of atherosclerosis and their caregivers face a high-stakes decision on statin treatment, with no clear direction from current guidelines.

The meta-analysis of Savaresi et al. (10) in this issue of the Journal clearly answers the question of whether statins reduce events in primary prevention of individuals age 65 years
or older. The reduction in the risk for MI was almost 40% and for stroke was almost one-quarter, albeit with relatively wide confidence intervals. All-cause and cardiovascular mortality were reduced by 6% and 9% respectively, differences that were not statistically significant.

The discrepancy between the results for MI and stroke on the one hand, and mortality on the other, is at least partly a consequence of different trials that were included for different endpoints. Approximately one-half of the weight for the mortality outcomes was from the ALLHAT (Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) trial, where pravastatin did not improve outcomes, a finding attributed to the narrow LDL-C difference between treatment groups (11). The ALLHAT trial was not included in the analyses for MI or stroke because those data were unavailable.

On the other hand, of the 5 trials included in the MI and stroke analyses, and of the 7 included in the mortality analyses, 3 were stopped early due to benefit. Not surprisingly, these were the trials that used the more potent statins, atorvastatin and rosuvastatin. Stopping these trials early limited the contribution that they made to the meta-analysis.

The findings of the meta-analysis apply to patients similar to those enrolled in the trials; their mean age was 73 years, and both women and men were well represented. All had risk factors in addition to age: hypertension, diabetes, low high-density lipoprotein cholesterol levels, high LDL-C levels, or high C-reactive protein levels.

Older people differ more among themselves than younger people do in many many ways, and the decision to treat or not treat an older individual with a statin often requires clinical discernment. The clear results of this meta-analysis will hopefully lead to more older individuals receiving treatment that will reduce their CV risk.

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