Statins, Primary Prevention, and Overall Mortality

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In November 2013, the American College of Cardiology and the American Heart Association published an update to cholesterol guidelines that sparked lively debate about the role of statins in the primary prevention of cardiovascular disease. Statin therapy reduces illness (stroke and myocardial infarction) (1), but attendant harms have been underappreciated (2). One measure of efficacy that is universally considered important is the effect of therapy on overall mortality (1, 2). Only 1 trial (3) among dozens has shown strong evidence of a mortality benefit with statin therapy, and the study was criticized for early stopping (4). Small differences in all-cause mortality may be difficult to capture in individual trials but may be important on a population-wide level. Meta-analyses are well-suited to clarify this issue. In fact, Taylor and colleagues' updated Cochrane review in 2013 found that statin therapy decreased all-cause mortality by about 14% (5).

Their meta-analysis included 13 trials that reported mortality outcomes. They excluded studies in which more than 10% of participants had cardiovascular disease at baseline to avoid biasing the analysis in favor of treatment. Including secondary prevention patients, who already have an indication for treatment, is a challenge in meta-analyses that try to pinpoint the effects of statins for the general population. Such patients are included in several randomized trials, and outcomes derived from them may skew results. Some authors have used alternative strategies to tease out information relevant to primary prevention from the existing trials. In a 2010 meta-analysis, Ray and coworkers queried primary study authors, obtained individual-patient data, and meticulously excluded secondary prevention patients while examining the effect of statins on mortality rates (4). In doing so, they considered at least 2 trials that the Taylor meta-analysis could not and also more precisely identified primary prevention patients in at least 1 other study.

The **Table** shows a comparison of trials reviewed by Taylor versus Ray. Of 17 studies, 4 were identical in both publications, 3 had discrepancies in the number of deaths or sample size, 6 were unique to Taylor, and 4 were unique to Ray. The number of deaths ascertained among statin and placebo users was 1077 and 1223, respectively, in Taylor and 1346 and 1447, respectively, in Ray. The mortality rate for statin and placebo groups was 4.41% versus 5.17% in the Taylor analysis and 4.13% versus 4.44% in the Ray analysis. Although Taylor noted a significant risk difference in favor of statins by 0.76%, the difference of 0.31% captured by Ray failed to meet significance in that analysis. Less than half of a percentage point marked the difference between these conclusions: "Meta-analyses now provide extensive evidence that statins reduce . . . total mortality" (1), and "Data from a meta-analysis . . . showed no reduction in mortality associated with treatment with statins" (2).

What does the comparison of these meta-analyses tell us? First, the outcome in question—overall mortality—is important, and independent teams have made tremendous efforts to comprehensively estimate this outcome. Second, the ascertainment of mortality varies between studies nearly as much as the groups within each study. Comparing mortality rates between the placebo groups of the 2 analyses reveals a difference of 0.73% (5.17% vs. 4.44%; $P < 0.001$), suggesting that the control groups are different.

Close examination of the 2 meta-analyses uncovers several additional differences. Three trials reviewed by both groups differed in the number of participants or deaths. Differences reported for WOSCOPS (West of Scotland Coronary Prevention Study) (**Table**) were substantial—numbers diverged by several hundred deaths and participants. This trial originally included patients with angina and electrocardiographic evidence of coronary heart disease; Ray was able to exclude these patients but Taylor was not (4). In addition, Ray used outcomes from this trial at the end of randomization (4.9 median years of follow-up) (6), but Taylor used long-term outcomes that extended 10 years beyond the trial's completion, after unmasking and open-label use (7). Two other trials differed only in the number of deaths, which suggested that data were captured at varying durations of follow-up.

Of the trials unique to each meta-analysis, some may be questioned. In Taylor, 1 trial (CERDIA [Cerivastatin in Diabetes]) switched statins midstudy when cerivastatin was withdrawn. Two trials (ACAPS [Asymptomatic Carotid Artery Progression Study] and METEOR [Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin]) mandated some degree of carotid intimal artery thickening; whether this represents true primary prevention can be debated. One trial (KAPS [Kuopio Atherosclerosis Prevention Study]) included fewer than 10% of patients with a history of myocardial infarction, but individual-patient data were not used. Another trial (Bone and colleagues) mandated diminished bone mineral density, although it is unclear how this would affect results. One of the trials unique to Ray (HYRIM [Hypertension High Risk Management]) excluded patients who had switched to a vegetarian diet or a diet rich in Ω-3 fatty acids, which precludes assessment of whether drug therapy provides benefit beyond lifestyle modification. Three trials (ALLHAT [Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial], ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial], and PROSPER [Prospective Study of Pravastatin in the Elderly at Risk]) seem eligible only through use of individual-patient data.

Table. **Comparison of Clinical Trials, Participants, and Deaths Included in Meta-analyses**

Variable, by Trial (Year)	Deaths/Participants in Taylor et al, 2013 (5), *n/n*		Deaths/Participants in Both Meta-analyses, *n/n*		Deaths/Participants in Ray et al, 2010 (4), *n/n*	
	Statin	Placebo	Statin	Placebo	Statin	Placebo
Same data						
AFCAPS/TexCAPS (1998)	–	–	80/3304	77/3301	–	–
CARDS (2008)	–	–	61/1428	82/1410	–	–
JUPITER (2008)	–	–	198/8901	247/8901	–	–
ASPEN (2006)	–	–	44/959	41/946	–	–
Discrepant data						
PREVEND IT (2004)	10/433	8/431	–	–	13/433	12/431
WOSCOPS (1995)	619/3302	674/3293	–	–	88/2998	113/2983
MEGA (2006)	55/3866	79/3966	–	–	43/3866	66/3966
Unique to Taylor et al						
Bone et al (2007)	0/485	0/119	–	–	–	–
CERDIA (2004)	3/103	4/79	–	–	–	–
ACAPS (1994)	1/460	8/459	–	–	–	–
KAPS (1995)	4/214	3/212	–	–	–	–
METEOR (2010)	1/700	0/281	–	–	–	–
PHYLLIS (2004)	1/253	0/254	–	–	–	–
Unique to Ray et al						
ALLHAT (2002)	–	–	–	–	521/4475	513/4405
ASCOT (2003)	–	–	–	–	155/4391	156/4324
PROSPER (2002)	–	–	–	–	139/1585	135/1654
HYRIM (2005)	–	–	–	–	4/283	5/285
Total*	1077/24 408	1223/23 652	–	–	1346/32 623	1447/32 606
Deaths, %	4.41	5.17	–	–	4.13	4.44

ACAPS = Asymptomatic Carotid Artery Progression Study; AFCAPS/TexCAPS = Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; ASPEN = Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes; CARDS = Collaborative Atorvastatin Diabetes Study; CERDIA = Cerivastatin in Diabetes; HYRIM = Hypertension High Risk Management; JUPITER = Justification of the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS = Kuopio Atherosclerosis Prevention Study; MEGA = Management of Elevated Cholesterol in the Primary Prevention of Group of Adult Japanese; METEOR = Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin; PHYLLIS = Plaque Hypertension Lipid-Lowering Italian Study; PREVEND IT = Prevention of Renal and Vascular Endstage Disease Intervention Trial; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; WOSCOPS = West of Scotland Coronary Prevention Study.

* Totals are the sum of the data in the Taylor and Both columns, and the Ray and Both columns. For example, the statin-related deaths data in Taylor (n = 694) plus the stain-related deaths data in Both (n = 383) equals 1077 deaths.

Results that seem to conflict can sometimes be adjudicated by additional analyses. In 2012, the Cholesterol Treatment Trialists' Collaborators found in a study of more than 134 000 patients that, among persons without vascular disease, statins reduced the risk for all-cause mortality for each 1.0-mmol/L (38.61-mg/dL) reduction in low-density lipoprotein cholesterol level (rate ratio per 1.0-mmol/L [38.61-mg/dL] reduction, 0.91 [95% CI, 0.85 to 0.97]) (8). However, analyzing mortality rates weighted by trial-level low-density lipoprotein cholesterol reduction is flawed because it places more weight on trials with greater decreases in cholesterol level (9). The authors also analyzed overall mortality in trials of statins with varying potency and dose together with trials of statin versus placebo. As such, I do not believe that the Cholesterol Treatment Trialists' study can adjudicate whether statins improve survival for primary prevention patients.

When the final count matters, and the results are close, recounts are commonplace. Eighteen states mandate automatic recounts in tight political elections (10), typically when the number of votes differs by less than 0.5%. For statins in primary prevention, 2 meta-analyses draw opposite conclusions, although they also differ by less than 0.5%. With results this close, is it time for a recount? All published and unpublished trials may be brought forward, and individual-patient data should be made available from studies in the **Table** that include secondary prevention patients. The Cholesterol Treatment Trialists' study has a robust set of deidentified individual-patient data, which can improve our understanding, and those data should be made widely available. Updated results should be considered. For example, JUPITER (Justification of the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) was halted at a median follow-up of 1.9 years (3) after showing a statistically significant reduction in overall mortality. Although the trial was unblinded at the time, subsequent mortality data would be interesting to review because early stopping is known to inflate estimates of benefit.

Considering all data on a question of interest is fundamental to the appraisal of medical evidence. The approach described here may be used during the next

Cochrane review or under the direction of motivated independent investigators. In either case, examining results using better methods will provide clarity. Debate surrounding guidelines is inevitable because complex data are translated into specific recommendations, but all parties share an interest in having the best facts at hand to inform that debate. A profession-wide commitment to reviewing all data may improve our understanding of the fundamental question: Can statin therapy improve the longevity of patients who feel well but are at risk for cardiovascular events and have not yet experienced them?

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