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Point/Counterpoint

Point: Why statins have failed to reduce mortality in just about anybody

This discussion was sparked by an editorial critique by Sniderman et al[1] regarding the 2010 Cholesterol Treatment Trialists' (CTT) meta-analysis that suggested a statin "event" benefit from maximal lowering of low-density lipoprotein cholesterol levels.[2] There are two issues that deserve further attention: the components of the CTT study end points and, most importantly, the issue of reduction in all-cause mortality.

The weakness of the CTT meta-analysis end points: the chosen "events"

Sniderman et al highlighted the fact that more than 50% of all "event" benefit in the "lower is better" 2010 CTT analysis was from fewer revascularizations performed. This is the least "hard" of the end points assessed, as was recognized by Sniderman et al in their commentary. Indeed, the softness of this majority end point is illustrated by the following 2 examples:

1. A study reporting on 28,825 patients and 106 hospitals found that 90% of revascularizations were avoided by the patient first presenting to a closer noncatheterization-laboratory equipped hospital and that, by doing so, mortality was significantly lower 6 months after the presenting acute coronary syndrome.[3] This finding is consistent with the performance of this procedure as a response to the patient's symptoms and not to definitive objective findings.
2. In JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial), a trial involving 17,802 participants randomized to rosuvastatin or placebo, investigators reported a highly significant reduction of nonfatal myocardial infarction and stroke; however, the only statistically significant benefit from the statin for women was from fewer revascularizations, whereas for all participants the cardiovascular mortality was not reduced ($P = .37$).[4] Again, this leaves open the question of whether a life-threatening acute coronary syndrome was treated or simply the patient's symptoms.

Statins are known to improve vascular reactivity in studies of flow-mediated dilation of muscular arteries and to reduce angina pectoris over time. This improvement probably results from the enhancement of the nitric oxide/endothelial nitric oxide synthase system that is involved in the maintenance of smooth muscle cell relaxation and optimal compliance of muscular arteries,[5] which raises the question of whether the elective revascularizations might have been reduced as the result of improved vascular compliance and the associated reduction in chest pain attributed to angina. This finding would imply that the often-assumed reduction of lesion size and change in lipid composition may not have been the reason for reduced revascularization procedures. Consistent with this hypothesis was the observation that fatal infarcts were not reduced.[4]

All-cause mortality with the use of statins in women

It is still commonly assumed by patients, authors, and doctors that statins are "life savers," but is this really the case? The need for studies that could answer the question of total mortality reduction with cholesterol reduction was called for many years ago[2,6,7] and required larger and longer comparisons of treated versus placebo-controlled groups. In addition, the existence of benefit in groups such as women and older patients was questioned[7] All published trials with placebo controls conclusively establish that statins do not reduce mortality in women and, in the CTT meta-analysis, the only thing reported was the "proportional coronary heart disease mortality."[6]

Some Trialists have expressed the opinion that total mortality is a rather unhelpful [sic] end point in cardiovascular prevention studies because one is assessing a number of deaths that may have no relationship to atherosclerosis-related causality. The authors of the CTT meta-analysis have previously referred to all-cause mortality as an "insensitive measure" of the benefit of statins (*Lancet*. 2012;380:1817). One would hope that treatment with statins to prevent major cardiovascular disease could show benefit in this important end point considering that,

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in the 2008 European Cardiovascular Disease Statistics, 54% of women and 43% of men died from cardiovascular causes.

Recently, a meta-analysis by Kostis et al also noted the weakness of the mortality data for the Anglo-Scandinavian atorvastatin study (ASCOT-LLA).[8] This study ended with two more undefined "events" in women on atorvastatin than on placebo.[9] During the ASCOT-LLA study, the population assigned to the placebo did numerically better at a mean study duration of 1.7 years, whereas at 3.3 years the mortality curves did not differentiate.[9] Recently, there were calls for more trial transparency. Determining the number of persons needed to treat to prevent one death is exceedingly important because we spend billions of dollars for statin therapy in millions of patients.

It is widely reported that approximately one half of the patients on statins stop them after 1 year. This is why we need the year-by-year mortality data and those are simply not reported for the most relevant studies. Moreover, in two of the major clinical trials that did report successful reduction in total deaths (for men only), 4S and the HPS (Heart Protection Study), the mortality curves begin to separate only after 1.5 years. The message for younger, high-risk men is that unless they plan to take statins for at least 2 years, there is no shown impact on longevity. There are no mortality figures suggesting a positive effect for people taking statins for more than 5 or 6 years. In the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) study, in patients older than 70 years of age, there appeared to be arising increased rate of cancer, which may indicate that longer intervals of therapy may have other costs in the elderly.[10,11]

For women, all published trials have failed to demonstrate decreased mortality when therapy with statins has been compared with a placebo. For both genders, the lack of all-cause mortality benefit is also illustrated by all published studies using atorvastatin vs. placebo, including the summary of 49 in-house studies including 14,236 individual patients.[12] The secondary prevention study SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) ended with five more deaths on high-dose atorvastatin than on placebo (31 in 1). To date, there are no placebo-controlled studies showing a mortality benefit when patients used lovastatin, fluvastatin, cerivastatin, or pitavastatin. This is true for rosuvastatin as well if one discounts the finding of fewer cancer deaths in the treated group in JUPITER. Moreover, no mortality benefit has ever been shown in patients older than 70 years of age (the study-group of the PROSPER study), in patients with heart failure (ie, CORONA [Controlled Rosuvastatin Multinational Study in Heart Failure] and GISSI-HF [Gruppo Italiano per lo Studio della Sopravvivenza nell Infarto Miocardico–Heart Failure]) and in patients with kidney failure (AURORA [A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events]). Clearly therefore, meta-analyses that blend patient groups, ages, and genders cannot change the lack of mortality benefit findings in the individual statin studies.

The trouble with meta-analyses: the relative risk (RR) issue

Rather than reporting numbers needed to treat, per year, per end point, per patient type, and with 95% statistical confidence limits, CTT and similar analyses[2,6,8] provide RRs, proportional risks, and heterogeneity data and are typically illustrated by RR "forest plots", all metrics of limited value to patients most interested in whether the use of statins will reduce their absolute risk of dying prematurely. Basing estimates on the 2005 CTT analysis, which blends genders and patient groups, one would have to treat approximately 1900 patients (54% with vascular disease upon study entry and 57% cardiovascular deaths at the study end) with statins for approximately 1 year to extend the life of one person. Statistical significance loses all meaning in this context because the finding is obviously not clinically relevant, as the absolute benefit is extremely small and not applicable to women and to the other patient groups mentioned.

The place of statins in atherosclerosis prevention

Patients believing consciously or subliminally that "their cholesterol is under control" because they take a statin may postpone embarking on lifestyle changes, such as stopping smoking and abandoning eating habits that produce obesity and diabetes. In addition, there is evidence that statins by themselves promote diabetes, a life-long health risk. Because the lack of circulating statins is not the cause of atherosclerosis and their benefit on mortality is highly questionable, we should concentrate on lifestyle changes. Exercise, no smoking, and a healthy diet are well demonstrated in population studies to reduce the high mortality seen in so many economically developed countries.

In summary, and in support of the Sniderman et al's article that "lower and lower may not be better and better," we must question the way statins work because they effectively do not prevent cardiovascular and all-cause deaths.

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Counterpoint: Statins do reduce fatal events

Vos et al title their article ‘”Why statins have failed to reduce mortality in just about anybody.”[1] The simple, straightforward, uncomplicated, and direct answer to their question is that they do. My colleagues and I did critique several conclusions of the Cholesterol Treatment Trialists (CTT) 2010 meta-analysis, but we did not challenge the evidence therein that statins reduce both cardiovascular mortality as well as total mortality.[2] Moreover, the investigators from the Heart Protection Study (HPS) demonstrated that all-cause mortality was 14% lower as the result of a 17% reduction in cardiovascular mortality in the 10,269 patients treated with simvastatin compared with the 10,267 who were allocated to the placebo arm.[3] The 2005 CTT demonstrated a 12% reduction in all-cause mortality per mmol/L reduction in low-density lipoprotein (LDL) cholesterol, which was driven by a 19% reduction in coronary mortality.[4] Brugts et al[5] also demonstrated reductions in all-cause mortality in their meta-analysis.

Vos et al state that: “All published trials conclusively establish that statins do not reduce mortality in women.”[1] This statement also is not correct. Taylor and Ebrahim,[6] in a commentary written in response to a meta-analysis by Gutierrez et al,[7] who demonstrated similar reductions in coronary events in men and women with statin therapy but did not identify a significant benefit in women for strokes and all-cause mortality, are particularly persuasive. They point out that Gutierrez et al did not include all relevant studies in their meta-analysis. In addition, Taylor and Ebrahim note the positive findings of Walsh and Pignone[8] of a reduction in cardiovascular events in women with cardiovascular disease as well as those of the meta-analysis by Kostis et al,[9] which was larger and therefore more powerful than that by Gutierrez et al and that demonstrated significant reductions in both cardiovascular events and all-cause mortality in both men and women. Moreover, the CTT 2010 analysis[10] showed similar reduction in major vascular events in women as in men and, to complete their tour de force, by adding the results of HPS, which has more events, to those of Gutierrez et al, Taylor and Ebrahim show the decrease in all-cause mortality is virtually the same in women as in men. Bravo.

Vos et al[1] do support our critique of revascularization as an end point but not in the sense that we made it.[2] We did note that revascularizations are not as “hard” an end point as death or myocardial infarction, a conclusion we believe all would agree to. However, we did not deny they are an end point, nor did we deny the evidence that statins reduce the rates of revascularization. Our point was that not all end points have the same clinical significance or freedom from bias and net estimates of benefit should take that into account.

Vos and his colleagues conclude that the principal mechanism of action and of benefit of statins is a nitroglycerin-like effect via stimulation of the nitric oxide/endothelial nitric oxide synthase pathway.[1] Indeed, there is a sizeable literature in which the authors explore multiple, potential, non–LDL-related mechanisms of benefit of statins but, in our view, there is no convincing evidence for the positive claims although, admittedly also, no logical way to definitively exclude them. Nevertheless, the correlation between benefit and reduction in LDL is so strong[2] that it is hard to imagine a sizeable, non–LDL-related, independent mechanism of benefit. Statins lower LDL, and LDL is the prime driver of atherosclerotic lesion formation and maturation. Brown and his colleagues deserve inestimable credit for the FATS (Familial Atherosclerosis Treatment *Study*) trial,[10] which, by using quantitative coronary angiography, a technology that Brown led in developing, they demonstrated that statins reduced the rate of lesion development and this related to clinical benefit. If there were no other reason to write this note than to celebrate their achievement, that would more than justify it.

But there are two more points we wish to make briefly. First, however critical we are of the specifics of the note by Vos et al,[1] we are not critical of their right to produce it because the right to challenge conventional wisdom is a core commitment of science. Whether the sequence is claim and confirmation or claim and rebuttal, the search for knowledge is a sequence of acts. Too often, “discoverers” seem to claim an exclusive right to interpret the soundness and significance of their findings. Too rarely do we acknowledge that testing knowledge is vital to establishing the validity of knowledge.

The second point is that we must recognize, forthrightly and unambiguously, the reality that the evidence from clinical trials will always be incomplete and we must come

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to grips with what this means for guidelines and clinical decision-making. As summarized in the preceding paragraphs, the evidence for clinical benefit in both men and women with symptomatic vascular disease or at high risk of vascular disease is conclusive. That said, the evidence for reductions in mortality in primary prevention in low- to moderate-risk subjects does fall short of being unequivocally conclusive.[11,12]

Does that mean we should not use statins in primary prevention? Not at all. It just means that we must think about whether we should or we should not. We need to remember that the vast majority of the clinical decisions we make are not determined by conclusive randomized-controlled trial data. Evidence-based medicine is not clinical medicine. Not acting, not using statins in primary prevention is as real an act as using them. As a first principle, we must acknowledge that evidence never has been and never will be complete. Accordingly, whatever their pretensions, all guidelines can be no more than the best approximations of what the participants think the incomplete evidence at the time shows. Without intending to or even realizing we are—we transform evidence—the specific results of specific experiments—into general concepts and these concepts, inevitably, will not capture the full truth. Three recent examples: the Cochrane report that treatment of mild hypertension, ie, 150–159/90–99, has not been shown to be of clinical benefit[13]; the analysis that beta-blockers in patients with stable coronary artery disease may not produce clinical benefit[14]; and, if we may be excused, our critique in the pages of this *Journal* of the concept that "Lower and Lower is Better and Better."[2] Simply put, there are no clinical trial data demonstrating that atorvastatin 80 mg daily produces significantly fewer clinical events than atorvastatin 40 mg daily or, for that matter, atorvastatin 20 mg daily, just as there are insufficient (although not no) clinical data establishing the value of targets.[2] Guidelines can recommend atorvastatin 80 mg as the preferred dose on the grounds that it has been tested against atorvastatin 10 mg but not on the grounds that there is evidence that atorvastatin 80 mg daily is superior to the intermediate doses of atorvastatin. Unfortunately, the studies, which compared statin doses at the extremes, appear designed to affirm the hypothesis that lower is better, not to test it, and consequently, we admit, there are no data demonstrating intermediate doses of statins are more effective than lower doses.

Does this mean we should throw up our hands and do whatever we are told to do? No. It just means that we physicians should recognize that acting on incomplete information is our professional métier. It is what we do. We should recognize that the evidence from clinical trials, although invaluable, is not the only form of evidence. Observational studies, including registries, physiology, our own clinical experience, and skills—yes, these forms of evidence are limited and certainly subject to error—but they are far from useless. Indeed, in our current information overload age, critical thinking, medical strategies that begin with the results of randomized clinical trials but are also physiologically and epidemiologically coherent, strategies that are crafted for the individual patient, strategies that are the products of clinical reasoning have never been needed more. We hope we have been able to reassure Vos et al about the concerns they raise. The fact is that if their requirement for action were to be accepted—that the very last piece of evidence must, always, already be in place before any decision can be made—then the first step to help anyone will never be taken.

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Rebuttal: Why statins have failed to reduce mortality in just about anybody

It is unfortunate that in their Counterpoint Sniderman et al digress from the issue of mortality. To reiterate, all trials in which investigators used a placebo in women failed, as stated in the Counterpoint from a reference by Walsh and Pignone[1]: "For all trials reporting total mortality, lipid lowering did not appear to have a beneficial effect for women with or without previous cardiovascular disease over the 2.8 to 6-year study period in the available trials." The relative risks were 1.00 and 0.97, respectively. Here, too, numerically the most "benefit" was in fewer revascularizations performed, but this in the secondary prevention group only [number needed to treat (one year) = ~140]. That's it. Adding another 40,000 on-statin women patient-years to the trial database cannot change this fact of mortality benefit failure.

Indeed, the article by Brown et al[2] referred to in the Counterpoint showed impressive images of arteries opening (arguably by delipidation of lesions), but there was only one death in this study (n = 146) in which the patient used either lovastatin, 30 grams of bile acid sequestrant per day, or a mega-dose of high-density lipoprotein–increasing vitamin B3, niacin, arguably the only promoter rather than inhibitor of biochemistry in cholesterol-affecting studies. Unfortunately, in this type of study one cannot tell whether an artery has stronger fibrous caps because cholesterol itself has no known role in the synthesis of the relevant arterial and cardiac proteins, structural collagen, and architectural elastin. If any symptom relief was obtained, as it well may have, this could lead to a few less elective revascularizations performed during such 30-month study length. However, all this distracts from other potentially life-saving causal avenues of research. It also distracts from the failure of our six-decades-old "war" on cholesterol to have saved lives.

Clinicians should remain mindful that without yearly numbers needed to treat, nonfatal relative risks and surrogate measures do not represent life extensions in what is still our most fatal type of disease—cardiovascular disease—and that the easiest to count and often-hidden end point is all-cause mortality in patient groups, witness: The Cholesterol Treatment Trialists' Collaboration.

We maintain that statins have not been demonstrated to be life-extending drugs except, possibly and for a brief window of time (years), in younger, high-risk men. We could say it no better than paraphrasing the cited Heart Protection Study[3] and Cholesterol Treatment Trialists'[4] collaborators, who noted that mortality is a rather *insensitive* and *unhelpful* end point in statin trials, an elegant but roundabout way of bluntly stating that statins have conclusively shown not to save anybody's life.

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