LETTER TO THE EDITOR


To the Editor:
Fitchett et al have presented supporting evidence for the ‘lower LDL-C is better’ concept.

Much of the proposed benefit is in events, however defined, and that may include silent heart attacks, hospital interventions and angina. For example, event benefit in ASCOT (1) included a 41% reduction in stable angina, a nonfatal pain but a pain that may well cause fewer hospital visits and catheterization laboratory-generated interventions. Such event reductions could therefore simply result from the nitroglycerin-mimicking action (promoting the NO-synthase pathway) of statins – and when nitroglycerin is the treating agent of choice.

Moreover, ‘event’ benefit may only be found in some groups, such as men before their sixties, while actual medical benefit, such as fewer myocardial infarctions (MI) and fewer deaths, is never found in women and often not in others, for example, in the post age 70 patients who comprised PROSPER (references in 2), and when mortality was not improved and new cancers significantly increased (P=0.02).

The two main problems with the lower-is-better concept and the suggested 12% lowered mortality (in any patient) for 1 mmol/L LDL-C reduction after five years of statin use (3) are illustrated by the following:

- When comparing atorvastatin with placebo in ASCOT, we find that up to the median study end of 3.3 years the mortality curves simply do not separate, while the recently published SPARCL trial found five fewer deaths after 4.9 years in patients on a placebo than in those on top-dose atorvastatin (4). Ominously, the study discussed, TNT, ended with two more deaths on the top-dose versus the lowest-dose atorvastatin, the final nail in the coffin of any hope that atorvastatin, or increasing doses thereof, may possibly extend lives. Incidentally, ASCOT also ended with two fewer Mls, one fatal, in women taking a placebo.

- Patient outcomes also call to question the lower-is-better concept, when possibly the largest follow-up study in hypercholesterolemic patients (n=41,801, six years, taking simvastatin) finds doubled mortality in patients with the lowest LDL-C and quadrupled mortality in those with lowest total cholesterol (Figure 1 [5]). The drug cost would have been approximately 1/4 billion dollars. The authors suggest caution in ‘hyper-responders’ (to statin), a caveat hard to square with what Fitchett et al propose.

REFERENCES
From the Authors:

Mr Vos’ comments highlight the need for randomized clinical trials with prespecified, clinically relevant end points. When such clinical trials are undertaken, the benefit and safety of statin therapy, including atorvastatin, are clearly demonstrated based on prespecified end points and recognized statistical analysis. This consistent and reproducible evidence that lower LDL-C levels, achieved through competitive LDL-C-lowering therapy such as statin therapy, are associated with improved outcomes in higher-risk patients, has now been recognized and incorporated into LDL-C-lowering guidelines around the world. When sample size or design of the study does not allow an evaluation of an important end point such as total mortality, we have to rely on available meta-analyses, although limitations of this approach should be acknowledged. The limitations are even greater when lower LDL-C is associated with higher mortality in epidemiological studies, because the bias of the comorbid conditions, particularly cancer, cannot be accounted for. In summary, the issue of whether lower LDL-C is better for our patients at higher risk of cardiovascular events has been resolved in clinical trials, and we now need to settle on reliable and cost efficient ways of delivering evidence-based care to our patients.

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