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LETTER TO THE EDITOR

Statins for women, elderly: Malpractice?

While de Lorgeril and Salen [1] call for a new paradigm excluding cholesterol, Trevisan and Stranges [2] call cholesterol lowering [to reduce mortality] ''a great success story!'' How to reconcile these points of view?

The 'statin success' story is largely from non-fatal endpoint studies that may well derive much of such benefit from reduced angina (and thus hospital visits and resulting interventions) via statins' well known nitroglycerin mimicking NO synthase pathway. Reducing angina and improving artery compliance may not affect mortality and this is indeed what is found in all studies reporting on women and in the one study targeting people over age 70, PROSPER, that ended with identical mortality between groups (±0.1%) and more new cancers on statin (references in Ref. [3]).

Regarding women, two 2004 analysis [4,5] found no reduction in deaths from statin over placebo. In actual patient outcomes, the 6 year 1/4 billion dollar (approximate simvastatin retail cost) J-LIT study in 41,801 hypercholesterolemic Japanese (2/3rds women; mean baseline cholesterol 7 mmol/L) found mortality in the 2 lowest on-statin cholesterol categories 2–3 times higher than in patients remaining near 6.4 mmol/L [6]; its authors cautioned about 'hyperresponders' to statin (Fig. 1). The 4S study ended with 3 more dead women on statin vs. placebo [7]; another 'successful' study, HPS, found no significant mortality benefit in women [8].

Commercial success for atorvastatin [Lipitor®] but how about mortality? Until mean study end, 3.3 years, the mortality curves touch in ASCOT [Medline 12686036] and the recent 5 year SPARCL trial [Medline 16899775] had 5 fewer deaths on placebo than on top-dose atorvastatin. Incidentally, ASCOT ended with 2 more heart attacks in women, one fatal, on atorvastatin. There are indeed no studies showing atorvastatin saves lives. Moreover, it does not slow arterial or aortic valve calcification (+26 ± 1% per year and +22 ± 0.3% per year, respectively [9,10], and Medline 16449511); the structural decline continues unabated notwithstanding this top-selling statin.

The cited data support removing women and older men from the cholesterol guidelines if extending life is a patient criterion [3], as well as the call for paradigm change. This call is not new; it follows the 1977 NEJM editorial ''Diet-Heart: End of an Era'' [11], years before statins put the cholesterol-as-cause hypothesis on costly life support only to have it, again, shown a failure in women and in most men at the age when vascular disease causes most deaths.

Interestingly, statins had a close call with their first mega-trial, EXCEL, ending with almost significantly more deaths on lovastatin than placebo and where, at 11 months, the drug's maker simply discontinued the placebo group [12]; lovastatin's final mega-trial AFCAPS/TexCAPS also ended with fewer deaths on placebo.

Unless one believes in the sanctity of only 2 studies, pharma-run 4S with unusual mortality curves and HPS with a rare on-drug run-in phase and yet unpublished 4 main group mortality curves, I would argue there are zero mortality benefit studies for any of the 8 statins that are or were. Is there a Giordano Bruno or Galileo in the house, or a female Joan of Arc to change the paradigm?

As new paradigm and in line with the name of this Journal, I'd propose long-term protein degradation by homocysteinylation and glycosylation, different topics where space restrictions do not allow me to go but where decades of research has shown consistent promise. Once arterial structural decline is present, in order to prevent sudden deaths, omega-3's [1] and magnesium supplementation are avenues deserving urgent attention.

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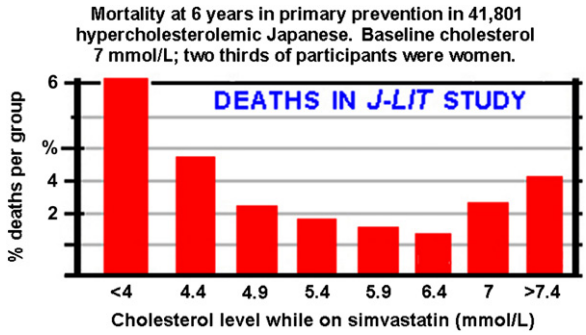

Figure 1 Graphic rendition by E. Vos of Table 5 of J-LIT study in Medline 12499611.

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