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When and Why Statins Fail to Save Lives

To the Editor:

The Commentary by Hennekens et al[1] about statins and diabetes makes suggestions about mortality that are not supported by most placebo-controlled trials. The opening sentence suggests that statins lower mortality in primary prevention and in diabetics, without being more group specific.

For instance, the concluding sentences suggest that "many" premature deaths will result when needlessly halting statins, or over concerns about diabetes, and that this is particularly alarming in women, where cardiovascular deaths are far and away the leading cause, and in whom statins are most underutilized.

However, the authors fail to note that there are no placebo-controlled trials in women of any cardiovascular risk that show a mortality benefit from statin; none. The authors downplay the JUPITER study, finding that statins promote diabetes in part because another rosuvastatin mega trial, HOPE-3, did not find that effect[2,3]—but not mentioned is the fact that there was no cardiovascular mortality benefit in anyone in these trials ($P = .37$, $P = .34$, respectively). JUPITER was in a population highly selected for metabolic syndrome because of raised C-reactive protein—and where the only statistically significant benefit for women was from fewer (mostly elective) revascularizations performed.

There is growing awareness that many—we propose most—nonfatal event benefits may be related to the undisputed fact that statins promote nitric oxide via the nitric oxide synthase pathways, thereby mimicking nitroglycerin (ie, nitrates).[4,5] Predictably, fewer nonfatal myocardial infarcts, ischemic strokes, and revascularizations should be expected in any study population where the nitric oxide pathways are promoted, vs a group receiving placebo, and this without expecting lowered mortality. Tellingly, there are no mortality-reducing placebo-controlled trials with atorvastatin, cerivastatin, fluvastatin, lovastatin, and pitavastatin. This realization also suggests that endogenously synthesized cholesterol (reduced by statins) may play little role in mortality and why statins would fail to effectively reduce mortality.[6] The authors should have been precise, for example, with numbers-needed-to-treat in specific groups, when suggesting that statins reduce mortality (or that stopping them would increase deaths), but the suggestion that statins prevent deaths in women is wrong, and women should be told.

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