Misinterpretation of trial evidence on statin adverse effects may harm patients

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Finegold et al., in their article, interpret the absence of average difference in rates of published adverse effects (AEs) for statins vs placebo in industry-funded randomized controlled trials (RCTs) as meaning that statins have approximately no side effects. This shows a lack of understanding of critical issues of effect modification, selection bias, and selective publication that have repeatedly contributed to underappreciation of drug AEs. The resulting flawed conclusion is likely to cause serious harm to patients.

1. Average neutrality in a clinical trial does not mean average real world neutrality. Trial participants self-select and are selected for characteristics that render them less likely to have AEs on statins (e.g. greater vitality, physical and cognitive function, less comorbidities and polypharmacy). Resulting nonrepresentativeness rises with age.

2. Average neutrality in a clinical trial does not mean that no one in the trial was harmed. For many outcomes, statins confer harm and help, in different groups. Statins’ prooxidant and antioxidant effects predominate in different groups, prooxidant predominance is tied to statin AEs, while antioxidant effects contribute to statins’ pleiotropic benefits. Net effect – apparent benefit, harm or neutrality – depends on the balance of participants with risk factors linked to greater harm vs greater benefit – and stain potency. Favorable as well as adverse statin effects are documented for proteinuria; cancer (JUPITER vs PROSPER); and glycemia (WOSCOPS vs e.g. PROVE IT-TIMI 22) (see discussion of duality).

Neither an average neutral effect in the happenstance of the sample(s) tested, nor the existence of benefit to some, undo harm in those who experience it, or abrogate need for concern for those harmed. For example, in our broadly sampled low-dose statin RCT, effects were neutral on average for glucose and muscle weakness. However, for each outcome, predictable subgroups experienced significant harms, with effects reproduced separately for simvastatin and pravastatin vs placebo (so, not attributable to chance).

3. One must ask the question to get the answer. Most RCTs have not systematically elicited information on many potential AEs – like fatigue, even though fatigue is among the most commonly reported statin problems by patients. Our study which was double-blinded, randomized, placebo-controlled did ask this question, and showed average harm. (Our study also provided evidence to suggest that the glucose rise on statins is likely adaptive, protecting cell energy, and glucose rise on statins in the elderly related inversely to the development of fatigue on statins.)

4. Once the question is asked, it is necessary for the answer to be published. Selective inclusion of favorable findings in industry funded trials has been amply documented, and consistent findings favor the funder’s drug in head-to-head statin RCTs. Meta-analysis simply adds false precision to biased estimates. Inclusion discretion/bias is particularly problematic for nonprimary adverse outcomes in industry funded trials – which comprise virtually all major statin trials. Indeed, even when adverse outcomes are the primary outcome, industry databases were found to have mysteriously omitted or erased from the record a number of serious and fatal AEs in the active drug group, with the apparent effect at least of falsifying the data. (One can only speculate as to intent.)

5. Recently, the definition of serious adverse events (SAEs) was revised to favor concealing many serious problems, allowing investigators to report only SAEs that they deem “related” to the drug and “unexpected” – thus presuming the outcome. (Cardiovascular events with Avandia could have gone unreckoned.)

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6. As a clinician, I encountered many patients whose doctors had failed to recognize, or had dismissed, a possible statin connection to their problem, to their grave detriment. One man had been hospitalized for months for undiagnosed progressive wasting (losing >70lbs), and remained on 80mg simvastatin when I arrived on the inpatient service – by then he was in intensive care requiring ventilator support with no apparent prospects for recovery. I stopped his statin and he was off ventilator support, sitting up, no longer phtotic, in just days. Recovery to discharge took longer, but occurred.

It is attitudes fostered by articles like this that, through misunderstanding of evidence, would have led that patient to remain on statins to die (and will cause others to do so). The death would not have even been recognized as statin-related. It is the hope of countering such harm that makes publication of this response (and others like it) imperative.

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**References**


