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STATINS AND MORTALITY

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Executive Summary: In considering whether a patient should be placed on a preventive medication, the focus should be on outcomes that balance risks and benefits to the patient–rather than outcomes that target one organ system. All-cause mortality is a relatively objective outcome that balances risks vs benefits to the patient–on an outcome that matters, arguably, most. Statins–widely prescribed medications that lower cholesterol–have been shown to reduce all-cause mortality in comparison to placebo in middle-aged men either with heart disease or at elevated risk for heart disease by certain metrics. However, no all-cause mortality benefit (nor trend to benefit) has to date been evident in randomized trials in the elderly (over age 70 or 75) or in women, even those at high cardiovascular risk; nor in those without elevated cardiovascular risk, even if middle-aged men. In these groups, any benefits to mortality from cardiovascular causes have been offset by distributed increases in mortality from other causes. Moreover, no evidence suggests, where all-cause mortality has been neutral, that all-cause morbidity fares better. Lipid treatment practices do not currently reflect these patient-focused considerations, with potential adverse consequences to patient outcomes and to health care costs.

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Context

Preventive medications are prescribed for the purpose of protecting the health of patients. Statins have been the best selling prescription drug class in the world[1], and include atorvastatin (Lipitor™) the best selling prescription drug in the U.S., the world[2] and in history[3].

All drugs have risks as well as benefits. Whether a drug should be prescribed relies upon a favorable balance of the two.

Indeed, before a drug can be cost-effective it must first be effective.

Effectiveness should be assessed, for preventive medications, not by cause-specific outcomes that are expected to benefit nor by surrogate outcomes (like cholesterol or blood pressure), but by outcomes that objectively and equitably balance risks and benefits to the patient.

There is strong reason not to rely upon intermediate markers, or surrogate outcomes–markers that are measurable and have been linked to health effects, and so are assumed to serve as a proxy for health effects. The reason is: they often mislead. Thus, premature ventricular contractions (PVCs) are linked to higher mortality; so drugs given to prevent PVCs were once popular–until it was ascertained that rather than preventing death, they increased total mortality and sudden arrhythmic death[4]. Higher HDL-cholesterol is linked observationally to lower mortality. Yet trials of a drug that successfully raised HDL, torcetrapib (added to atorvastatin), were stopped early due to an excess of deaths[5]. Hepatitis can reduce cholesterol–but that doesn't mean we should encourage its development as a therapy to forestall heart disease. These are a few among legion examples.

Again, then, what is sought are outcomes that account for the fact that the patient will experience all the effects of a drug; that not all effects may be favorable;

and that it is the balance of benefits vs risks to the patient, on hard outcomes of importance to the patient, that should be the focus. One especially important index that objectively balances risks and benefits to the patient is all-cause mortality. Whether a patient is alive or dead is a matter of generally low subjectivity–and incontrovertibly high importance. Studies suggest that this index is of particularly high importance to patients[6,7]. Statin treatment has been shown to clearly reduce all-cause mortality in clinical-trial equivalent middle-aged men who have documented heart disease–across a broad range of lipid values[8,9]. Trials of statins, in patients with heart disease that are dominated by men under age 70, have shown mortality benefit–the benefit appears to be driven by the men, since similar risk reductions have not been observed in women within these trials[8,9].

Statins may also reduce all-cause mortality in some groups predominating in middle-aged men without heart disease, but who are at high risk of heart disease–and/or who have markers for risk that statins may particularly target (beyond lipid levels). In the West of Scotland study, with exclusively men (and high preponderance of smokers), statin use led to a trend to mortality benefit, with a relative risk reduction of 22%, that approached significance ($p = 0.051$)[10]. Smoking is a potent oxidative stressor[11,12], and statins at low and moderate doses commonly have shown antioxidant effects[13] that help to mediate their benefits to endothelial function, plaque stabilization, antithrombotic effects and others of statins' pleiotropic effects[14-16].

The recent JUPITER trial[17] focused on people with high levels of inflammatory markers (high sensitivity C-reactive protein, or hsCRP > 2) without known heart disease or high LDL-cholesterol, a group reportedly reflecting about 4% of the adult population[18]. In this group, a 20% relative risk reduction in all-cause mortality was observed. (In this sample, the absolute risk reduction in total mortality was quite low, about half a percent (0.55%)[17], and high costs for treatment have been estimated, at $480,000 per life saved with brand name statin[18]–costs are lower when rates for a generic statin are substituted. But the direction of effect was favorable; and with the very large sample used–over 18,000–the effect was strongly significant.) Statins have typical anti-inflammatory effects[19-21], and a range of studies suggest a strong association of inflammation with cardiovascular disease. (Such studies include, for instance, findings that elevated white blood cell counts[22], and elevated C-reactive protein[23] predict higher incidence of cardiovascular events and death.) The significant increase in glycemia in the treatment group, and the potent association between insulin resistance/diabetes and heart disease, do contribute to remaining questions about impact with longer term use; but the short term outcomes were clearly on balance favorable.

Thus, statins have been shown to confer net benefit in selected groups–particularly middle-aged men with heart disease or selected risk profiles–at least those who are "clinical-trial equivalent"•. Statin treatment according to current guidelines, however, is not confined to these groups.

Women: Women, even those with heart disease or at high risk of it, have not experienced benefit exceeding harm as indexed by all-cause mortality in existing major clinical trials. Thus, the 4S and LIPID trials–which enrolled mostly middle-aged high risk patients with diagnosed coronary artery disease[8,9], showed significant benefits to all-cause mortality in the total sample, with relative risk (RR) of 0.70, 95% confidence interval (CI) 0.58-0.85 for 4S; and RR of 0.78, 95% CI 0.69-0.87, for LIPID. For women within these studies, however, the trends were approximately neutral (RR 0.95 for LIPID[25]) or minimally unfavorable (RR 1.12 for 4S, 95% CI 0.65-1.93).

Premenopausal women are at very low risk of heart disease, and in little need of cardiovascular protections. And in epidemiologic studies, for postmenopausal women (and in some studies also younger women), cholesterol, particularly LDL-cholesterol, does not show a relation to all-cause mortality, as it commonly does in men of comparable age[26-31]. Since the randomized trial data align with the observational data, in failing to suggest mortality benefit in women (or, therefore, benefit exceeding risk) with lower LDL-cholesterol observationally, or with lipid reduction experimentally, there is little legitimate justification for generalizing statin mortality effects in clinical trials from men to women. Certainly subgroups of women may be found in whom benefits dominate (offset, then, by other subgroups in whom harms do). However, in general treatment in women should rationally await identification of such groups. (Whether women with elevated markers of inflammation–high sensitivity C-reactive protein, or hsCRP–represent such a subgroup is not clear: sex-specific mortality outcomes were not presented in the JUPITER trial[17].)

• Subjects who show up to screen for enrollment in studies and clinical trials, particularly for preventive medications, differ from the general eligible population: they are commonly healthier, more frequently Caucasian, and more robust than subjects in the population they are taken to represent. Study inclusion criteria may aggravate discrepancies by relatively excluding prospective subjects with polypharmacy and comorbidities (and elderly subjects) who are more likely to have adverse experiences on drugs. The gap between the relevant population and the study sample is further widened by compliance run-ins: lower compliance, assessed on placebo, is linked to markedly worse health outcomes and mortality (about 90% higher mortality in one randomized trial)[24].

Influence of adherence to treatment and response of cholesterol on mortality in the coronary drug project. *N Engl J Med* 1980;303:1038-41.

Elderly: Elderly (over age 70), *even those with or at high risk of heart disease*, have not experienced benefit exceeding harm as indexed by all-cause mortality, at least according to the sole randomized trial to focus on this group, the PROSPER trial[32]. All-cause mortality with statin vs placebo was neutral (RR 1.0). Incidentally, all-cause morbidity was neutral as well (RR 1.0). For those who believe stroke and dementia hold a special position due to the character of their impact in the elderly, stroke risk was also neutral (RR 1.0) and there was no suggestion of benefit to cognition. Moreover there was a statistically significant increase in incident cancer in those given statins rather than placebo (hazard ratio 1.25, 95% CI 1.04-1.51)[32]. Again, these findings align with observational studies, which often fail to show higher total mortality with higher LDL or total-cholesterol in elderly over age ~70[31,33-38].

Indeed, in the oldest old, higher cholesterol has been linked to lower all-cause mortality, a finding not extinguished with adjustment for potential confounders[33,36,37]. Thus, according to one study, "Each 1 mmol/L increase in total cholesterol corresponded to a 15% decrease in mortality (risk ratio 0.85 [95% CI 0.79-0.91])."[39] While unmeasured confounders could contribute to this association, confounding cannot be presumed to fully account for this: key functions of cholesterol take on heightened importance in the older elderly (e.g., transport of antioxidants, support of cell energy), providing rationale for a causal difference in total mortality impact of cholesterol in this group. Moreover the concordance of observational with clinical trial data bolsters the authority of each–with both failing to link lower cholesterol to reduced mortality in the elderly.

Two caveats bear mention. First, in PROSPER the effects of gender and age cannot be disambiguated. Unlike most statin trials, PROSPER included a good fraction of women. One could speculate that the overall neutral effect could mask harm in women and benefit in men–but absent data, this cannot be presumed. Sex-stratified data on all-cause mortality from that trial are not available. Second, this study says nothing about elderly who previously developed CAD and may have only made it to age 70 because of lipid lowering therapy. Third, the mean age of the sample was 75. It is possible that those in the 70-75 age group, for instance, fare relatively better on average while those in the over 75 age group offset this, though again absent evidence this cannot be assumed. As was noted for women, subgroups of elderly may be found in whom benefits exceed risks and treatment is indicated (offset by other groups in whom harms predominate); but treatment should await identification of groups in whom benefits can be shown to exceed harms. (Whether high hsCRP, overall or up to some age, signifies a group with average benefits within those over age 70 remains to be clarified.)

Middle-Aged Men If Not at High Cardiovascular Risk: Finally, middle-aged men do not reap benefit exceeding risk, based on all-cause mortality evidence, even if their cholesterol values are adverse, if they do not have heart disease or certain markers of risk for it. The recent findings affirming that elevated hsCRP (an inflammatory marker) is an important marker for risk–and for mortality benefit with statins–is compatible with prior evidence. The LIPID trial, for instance, suggested that high baseline LDL cholesterol was not the necessary arbiter of who benefited from treatment[25]. And since statins inherently produce all their effects when they are given, one effect (such as LDL reduction) cannot be presumed to provide the foundation for effects observed when statins are administered.

Since cholesterol does serve key functions, there is need for evaluation of the impact of long-term effect of statin treatment–treatment that further lowers cholesterol–in those with low baseline cholesterol and elevated high hsCRP (or other risk markers that are linked to statin mortality benefit with short-term use). But in fact, there is need for evaluation of the impact of long-term statin treatment in all groups, since cholesterol may also be upregulated to accommodate needs, such as antioxidant transport needs–and high cholesterol may sometimes signal higher needs for its functions and products.

High Dose Statin Therapy: High dose statin treatment increases costs and risks of treatment[40]; but the balance of evidence suggests it does not generally benefit mortality even in subjects at high cardiovascular risk (those with existing cardiovascular disease). Thus, in a number of double-blind randomized trials in subjects with existing cardiovascular disease, no trend to all-cause mortality benefit with high potency statins (80mg atorvastatin) has been found, when compared with either lower potency statins (10mg atorvastatin[41] or 40mg pravastatin[42]) or placebo[43,44]. A single trial did show a strong and nearly significant trend to mortality benefit in patients treated with atorvastatin 80mg vs pravastatin 10mg, within 10 days after hospitalization for an acute coronary event. In this study, the total mortality RR was 0.72, 95% CI approximately 0.5-1.03, with the confidence interval estimated from a graph[45]. However another trial of atorvastatin 80mg relative to placebo in patients with acute coronary syndrome did not show similar mortality benefit (RR 0.94, NS, though there were differences between the studies)[43]. And risk ratios for all-cause mortality with high potency statins (relative to the comparator treatment) in other studies of patients with coronary or cerebrovascular disease were completely neutral – with RRs of 1.01[41], 1.0[42], and 1.02[44].

All-Cause Mortality - Comments: All-cause mortality is a pivotally important index. Not only is all-cause mortality itself of central relevance to patients, but–not surprisingly–it appears to parallel all-cause serious morbidity in lipid-lowering studies where both are appraised. If there is no trend to mortality benefit in patients of a given profile, then there is little rationale for treatment, if the patient is the unit of interest–as the patient should be.

Where mortality benefit is present but requires very large studies to be seen–as in the JUPITER trial of those with elevated hsCRP17–there are other questions. Real world users often show a different and less favorable risk-benefit profile than clinical trial enrollees. Will small absolute benefits be sustained when treatment is extended to the broader population with the less favorable risk-benefit profile? Small absolute benefits may be attenuated, lost or conceivably even reversed in broader real world users in whom polypharmacy, comorbidities and other differences may amplify the harm side of the equation. If costs per life saved are already high in clinical trial samples, what are these costs in real world users, in whom the risk-benefit profile may be less favorable? At least, however, in this case there is evidence to suggest that mortality benefits may exceed risk–in clinical trial equivalent subjects.

Mortality Benefits and Risks: Mortality benefits of statins, in groups who reap these benefits, are relatively focused in the cardiovascular domain. In groups who do not exhibit trends toward mortality benefit, any trend to cardiovascular mortality benefits is, tautologically, fully offset by distributed increases in deaths from other causes. The fact that the causes of these "other" deaths are distributed is consistent with the known widespread functions of cholesterol throughout the body. Moreover, though the offsetting "excess" deaths are not focused in one or a small number of domains, death is just as fatal if it derives from a range of causes, as if it is focused in one or a few that are clearly defined.

Guidelines Depart from Evidence: Current widely employed lipid guidelines[46], authored by persons with industry conflicts[47], do not reflect the considerations above. These guidelines advise treatment in groups for whom there is no suggestion from clinical trials that benefits to the patient exceed risks–groups including women and elderly with elevated lipid values, with or without heart disease or high cardiovascular risk. As evidence advances, subgroups within these groups may be identified in whom treatment is merited. This implies presence of other subgroups within these groups that, averaged with them, lead to neutrality–i.e. presence of subgroups in whom treatment should be contraindicated.

Conclusions: Middle-aged men (under age 70) who have diagnosed heart disease and are "clinical trial equivalent," and middle-aged men without diagnosed heart disease but with high hsCRP or selected other indices of high risk, may experience mortality benefit that on average exceeds harm from statin therapy. (For those within this group who have experienced a possible or probable adverse effect, such as myopathy, the risk benefit balance is not known–but is expected to be less favorable.)

For other groups, evidence has so far failed to show suggestion of benefit exceeding risk, indexed by total mortality–a hard outcome of importance to the patient, that balances risks and benefits of the drug, and that, where evidence is available, tracks all-cause serious morbidity. For women (even if with or at high risk for heart disease), for those over age 70 (even if with or at high risk for heart disease), and for middle-aged men if not at high risk of heart disease, there is no suggestion that benefit exceeds risk. This is true even in available published trials–drug company funded clinical trials, in which outcomes commonly fare better than in trials funded by others [48,49] and better than in real world use, often markedly so. While there certainly may be subgroups within these groups for whom benefits dominate (and, implicitly then, other subgroups in whom harms prevail), such groups have yet to be characterized.

The presence of guidelines that contravene the evidence–and endorse treatments in groups for whom evidence does not support net benefit–has adverse consequences. Implications extend to health care finances, as monies are directed, to the tune of billions annually, to statin treatment for groups in whom there is no expectation that benefits dominate harms. And implications extend to patients, as physicians–motivated by so-called "performance measures" and "performance pay" that rely on these flawed guidelines–more avidly impose these drugs on patients without expected benefits–sometimes against patients' health state preferences, and even where adverse effects have arisen (imposing their own, sometimes tragic cost burden).

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