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The importance of monitoring adverse events in statin, and other, clinical trials

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Expected absolute mortality benefits of statins are generally modest, even in those who reap them. This amplifies the importance of understanding statins' adverse effects (AEs). Once AEs occur, the tradeoff considerations alter: the reality of the adverse issue, against a hypothetical, generally low absolute likelihood of future morbidity/mortality benefit. Additionally, prospects for cardiac benefits with statins may be attenuated – conceivably reversed – in those with statin AEs. Particularly where mortality is neutral, or likelihood of benefit small, AEs are vital to understand. Randomized controlled trials (RCTs) have historically been poor at AE identification. Serious AEs (SAEs) must be (re-)defined to reflect all-cause serious morbidity: requiring SAE reporting only for events deemed 'unexpected' or attributable to the drug, presumes the study outcome. Active inquiry and analyses attending to effect modifiers – and aggregation of them – can improve RCT utility for AE detection. AE monitoring benefits study balance and cost–effectiveness, and is central to ethical performance of RCTs.

"Adverse event monitoring benefits study balance and cost–effectiveness, and is central to ethical performance of randomized controlled trials."

AEs & AE monitoring are important: in general & for statins

Monitoring AEs is vitally important, for all interventions – particularly preventive measures, including statins. It is only with good knowledge of risks as well as benefits that sound guidelines can be crafted, and informed decisions made by physicians and patients about drug use.

Statins are mortality neutral in many groups. They have not reduced mortality in women with heart disease; nor in the high-risk elderly including those with heart disease; nor in high-risk primary prevention (on meta-analysis of RCTs) [1,2]. Statins have mortality benefit in middle-aged men with heart disease – but the absolute magnitude of benefit should not be overconstrued – and is relatively modest. In the unique most favorable statin trial from the standpoint of mortality, 4S, all-cause mortality was reduced by 'a third' (relative risk) [3]. However, this was the difference between approximately 12% risk and 8% risk over the 5.4-year median follow-up. Most of this 'high-risk' sample would not have died, even without statins (over this time; we all eventually die). Most of the sample who would have died without statins, would also have died with statins. So even in this group, there is room for AEs to moderate who merits treatment.

Once an AE occurs, the tradeoff becomes the reality of an adverse issue, against a hypothetical, low probability future benefit. AEs can have profound quality of life implications, which patients often feel doctors underestimate [4,5]. Moreover, prospects for cardiac benefits with statins may be attenuated – or even reversed

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– in those with statin AEs. Statin muscle AEs (and likely other AEs, which correlate with muscle AEs) are linked to net pro-oxidant effects of statins [6]. Since statins' antioxidant effects contribute to many statin benefits – antiplatelet, antithrombotic, blood pressure lowering, endothelial function, plaque stabilization or anti-inflammatory – net pro-oxidant effects may signify attenuate – and conceivably reversal – of cardiovascular benefits. Thus the importance of AE identification to the risk–benefit profile may extend beyond the risk side.

Fully understanding morbidity and AEs is vital, especially if benefits to mortality are not expected or the absolute fraction who reap them is small. That makes AE and SAE monitoring critical. For clinical trials to be most helpful for harm assessment, SAEs must be defined to (again) mean all-cause serious morbidity. SAEs hitherto were used for any event that was life threatening or fatal, caused or prolonged hospitalization or was disabling. SAEs have been reconstrued, requiring reporting only of those deemed unexpected and potentially related to the drug (presuming the outcome). This devastates utility of SAE assessment in clinical trials (consider the serious cardiovascular event risk now recognized with Avandia®: these would be 'expected' in this population [diabetics] and presumed 'unrelated' to glucose improvement, so unreported). Until meaningful SAE reporting is restored, statin trials neutral for all-cause mortality should be presumed no better for all-cause serious morbidity – and indeed have been no better, in statin trials providing data on both [1]. In these groups, any reduction in death, morbidity and disability to the heart has been fully offset by distributed increases in deaths, morbidity and disability from other causes.

Clinical trials are poor for AE detection, but can be made better

Clinical trials often have low sensitivity for AEs. Self-selection [7], human subject protections, research design *desiderata* (such as compliance run-ins) and cost efficiency conspire to produce enrollment of persons at lower risk of harm – lower comorbidities, polypharmacy, not frail or oldest elderly. Lower baseline risk yields fewer AE cases and lower power to detect an increase in AEs, at a given relative risk increase. Nonenrolled persons may also have quite different relative risks of problems than enrolled groups, via effect modification. Indeed, they may even have increases in problems, where studied patients have shown reductions (consider statin data and proteinuria).

AE evidence need not come from clinical trials. Evidence for benefits must come from randomized trials to be clinically relevant: only if it can be documented with high authority that a group has statistical expectation of benefit compared with otherwise similar persons not on the drug, is it justifiable to recommend the drug to an individual within the group (particularly for preventive treatments). However, harms are important to an individual whether or not they arise on average in a group. Since all (or any) subjects within a study need not have the average (favorable) clinical trial effects, RCT risk estimates have no necessary implications for whether an adverse effect in an individual represents an AE of the drug. RCTs also cannot exclude an 'average increase' in an AE for groups that differ from the study group, due to effect modification.

However, large observational studies, the kind viewed as 'higher quality' (including prospective cohort studies), can be worse still for drug risk–benefit determination. Large healthy-user and healthy-tolerator effects for preventive medications (including statins) produce dramatic benefit–harm distortions [8,9].

Clinical trials have different limitations for demonstrating AEs. These arise from low sensitivity, effect modification and the fact that AEs matter even if they are not typical effects. On-off-on dechallenge–rechallenge experiences resulting in induction–amelioration–exacerbation/recurrence respectively, can have stronger implications for adjudicating possible AE causality in an individual (particularly but not exclusively in that individual) than mean RCT effects do – because typical effects are not what matter for harm in an individual. Drug AE documentation from RCTs has often lagged, by many years, reports of AEs from good quality cases (including statins).

Still, AE documentation from RCTs is vitally important. First, many scientists and clinicians fail to understand that RCTs' superiority for benefit determination do not translate to equivalent superiority for harm assessment – so absence of demonstrated average harm in a specific trial sample can carry undue weight. Second, failure of a RCT to show a significant average increase in harm in the study group by no means excludes a possible connection of that drug to that harm in an individual; however, when RCTs do show an increase in a harm, this has high internal validity – generally good authority that the drug can cause the AE (with caveats). Third, since RCTs are disadvantaged in harm detection (both for the reasons above – and since they are typically industry funded, providing expected risk–benefit distortion [10,11]); and since they are overrated in harm authority, special efforts are required to learn about AEs in RCTs. If such efforts are not undertaken, RCTs arguably lose ethical viability. Patients deserve risk–benefit information that includes risk, and participants deserve not to have their services used in procurement of strikingly imbalanced evidence.

Several approaches can enhance AE detection from clinical trials.

- Ask the question: passive reporting of adverse experiences is insufficient – symptom ratings should be used. Single-item self-ratings of symptoms have shown good validity, reliability, sensitivity to change and predictive validity for a large range of symptoms, sometimes superior to validated multi-item measures; and they have low subject burden. For AEs, a low threshold should be maintained for concern if there is a suggestion of an effect, but a range of features enhance prospects for causality in the setting of multiple measures: prior concern related to the symptom (e.g., case reports); symptom relation to mechanisms produced by the drug (e.g., reduction in sexual function was highly significantly related to change in LDL in our statin trial [12]; musculoskeletal symptoms to lesser drop, and higher baseline LDL) [13]; literature linking that symptom to mechanisms known for the drug (even if not measured in that trial [14]); similar effect with split halves analysis – or on more than one statin (if tested) [15], dose relation (if different doses are assessed); among others.
- Consider effect modifiers: common effect modifiers (that relate to increased risk of AEs in many groups) include older age, female sex, frailty, polypharmacy, reduced drug clearance, drug interactions and conditions related to mitochondrial dysfunction – including chronic multisymptom illness overlap conditions and metabolic syndrome factors [16]. Renal and liver disease may both alter drug distribution and be signatures of other problems that relate to increased risk. Higher doses also generally produce higher risk of AEs [16]. Higher or lower cholesterol (or HDL [17], or LDL [13] – baseline, final and/or change) can relate to development of effects, for different reasons.
- Recognize risks may be underestimated: real world harms in a specific group may be greater than a study suggests, even when that was the group studied. Particularly with frail/elderly/polypharmacy – typically under-represented groups – those who do participate should be presumed nonrepresentatively healthy and vital relative to nonparticipants [7].
- Aggregate risk factors: our analysis of rhabdomyolysis cases in one medical system in San Diego, CA, USA (not confined to statins) showed that presence of more than one risk factor was typical [18]. Consistent with implications of this, in our statin RCT, among those with older age, larger numbers of metabolic factors (which individually are linked to elevated risk) predicted greater rise in glucose on statins (relative to placebo) [19]. Similarly, individual risk factors [16] were associated with stronger trends to muscle weakness; but coupling risk factors yielded larger risk ratios – and unmasked significance in the RCT setting, despite the smaller numbers bearing both factors [15].

Our University of California, San Diego, Statin Study, despite low statin doses by modern standards (simvastatin 20 mg and pravastatin 40 mg, vs placebo), has provided first RCT evidence (girding observational reports) for effects on sleep [20], fatigue/exertional intolerance [13,21], weakness [13,15], tinnitus [14], sexual dysfunction [12], as well as aggression and blood pressure (reduction, most typically a benefit) [17] and has added to RCT understanding of AEs also reported by others (muscle pain [13], cognition, glucose [19] and testosterone reduction; a 20-citation limit precludes inclusion of references for all). It thus contributed evidence for a larger number of AEs, not only than any other RCT (to our knowledge), but indeed, more than most other RCTs combined. Heeding case data from patients to inform RCT questions, the will to address the question, thoughtful analysis as above, and lack of industry conflict for the study or principal investigator are likely germane.

The imperative of AE detection

Study participants have a right for AE detection to be addressed seriously, for their own benefit and to avert unwitting complicity in generating needlessly imbalanced risk–benefit information (RCT evidence already entails more than enough inherent imbalance). Patients have a right to know, in order to make an informed decision based on their healthstate preferences – which should be unfettered by physician badgering, misleading or coercing due to performance pay [1]. Patients also have a right to know so that when an AE arises, they can discontinue the drug if they choose – and have evidence to better argue with their doctor if they must [4]. Physicians need to know, lest they cavalierly dismiss a drug relation for AEs reported by patients, as our evidence shows they often do, for statin AEs [4]; and so those who care can oppose clinical practice guidelines that incentivize (with performance pay) badgering, misleading and pressuring patients to resume drugs that have caused them harm (sometimes with tragic consequences). Regulators have a right to know, to avert the needless delays in AE warnings that are typical. Since industry funded trials historically may not report less favorable studies (or findings within them) [11]; and may not honestly portray AEs in published trials, even in the rare case these are a primary focus [10], federally funded RCTs should demand particular emphasis on AE detection.

For preventive treatments, harm should receive at least as much attention as benefit – more, because trials are inherently disadvantaged in detecting harms – and because *primum non nocere* should be a core value, not an insincere afterthought. Presently, AE identification is the neglected stepchild – little studied, little disseminated, disadvantaged in studies. Many drugs once popular and now discredited serve as a small reminder: failure to prioritize AE detection has produced harm, suffering, and death – needlessly – to many, and will continue to do so until the study of AEs receives the attention that should, all along, have been recognized as its due.

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