

PERSPECTIVE

Statins Safety Signals: From Precautions to Proportionate Evidence-Based Labeling

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The recent Cholesterol Treatment Trialists' Collaboration meta-analysis provides the most comprehensive randomized evidence to date regarding statin-associated adverse drug reactions, substantially narrowing the list of harms confidently attributable to statins. Beyond its clinical implications, the analysis highlights important challenges in pharmacovigilance and regulatory risk communication. Precautionary labeling based on low-certainty evidence may inadvertently amplify nocebo effects, reduce adherence to preventive therapies, and contribute to avoidable cardiovascular burden, particularly among vulnerable populations.

We read the recent meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration, which provides the most comprehensive randomized evidence to date on adverse events attributed to statins.¹ By pooling individual participant data (>120,000 participants) across 19 placebo-controlled trials, the authors demonstrated that the most commonly reported non-specific adverse drug reactions (ADRs) listed in the product labels, including cognitive impairment, depression, sleep disturbance, and peripheral neuropathy, did not occur with excess risk in statin vs. placebo groups. The CTT analysis confirms that only a limited number of adverse outcomes are supported by randomized

evidence. Of the 66 prespecified adverse events, four events showed a statistically significant excess risk. The CTT analysis, therefore, substantially narrows the list of ADRs confidently attributed to statins. The four confirmed adverse events were: abnormal liver transaminases (annual excess risk: +0.08%), other liver function test abnormalities (annual excess risk: +0.05%), changes in urinary composition (annual excess risk: +0.03%), and edema/tissue swelling (annual excess risk: +0.07%). These excess risks were very small in absolute events (all <0.1% per year). In addition to clinical implications, the CTT work underscores important regulatory considerations.

First, the findings highlighted a growing epistemic tension in pharmacovigilance. Randomized controlled trials (RCTs) remain the gold standard for detecting adverse events that occur more frequently in treated participants than in comparators. Nevertheless, drug labels validated by many national and international regulatory agencies also include a series of ADRs supported by spontaneous reports consistent with a precautionary regulatory approach. Such events can therefore attain unwarranted rhetorical parity with harms established in randomized trials, despite markedly different levels of evidence. The population-level consequences of precautionary labeling warrant careful consideration: even marginal reductions in adherence to statin preventive therapies can translate into substantial increases in avoidable cardiovascular events, mortality, and societal costs. This underscores the need to distinguish between individual prescribing prudence driven by perceived or label-interpreted risks and broader collective cardiovascular benefits. In this context, while precaution is essential to pharmacovigilance and patient safety, when not proportionate to the strength of the evidence, it can itself become a source of harm, particularly when ADR risk communication amplifies uncertain or very low risks without adequate contextualization of individual and public health benefits. Moreover, vulnerable populations often have lower health literacy² and are more susceptible to alarmist or negatively framed risk information, meaning that excessive or insufficiently contextualized warnings can disproportionately affect these groups and further exacerbate existing health inequalities. This effect is particularly evident with

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statins, where lower educational attainment is associated with reduced primary prevention use despite equivalent cardiovascular risk increases.³

Second, divergent regulatory criteria can contribute to inconsistencies in ADR risk communication. For the European Medicines Agency, ADRs are included in the Summary of Product Characteristics once drug-associated causality is considered at least “possible” using a structured assessment such as the World Health Organization-Uppsala Monitoring Center criteria.⁴ Similarly, the US Food and Drug Administration requires a “reasonable possibility” of causal association for ADRs.⁵ For both regulatory agencies, the causality assessment process is based on key factors, including the temporal relationship, dechallenge/rechallenge, exclusion of alternative causes, case patterns, consistency, and biological plausibility. However, such causality assessments remain inherently subjective, especially when case reports lack clinical details and contextualization. While precaution enhances early signal detection, overly expansive labeling can inadvertently promote nocebo effects and reduce adherence, specifically for preventive therapies such as statins, where perceived risk strongly impacts treatment discontinuation. Indeed, a randomized n-of-1 study showed that most statin-attributed symptoms were also reproduced on placebo, yielding a nocebo ratio of 0.90, and that unsubstantiated negative statin-related communication led to an 11–12% increase in treatment discontinuation.⁶

Third, clinicians and patients often struggle to interpret the magnitude, certainty, and clinical relevance of listed ADRs when these are insufficiently contextualized. This lack of distinction can contribute to overestimating risk and underusing statin therapies.

We propose three targeted recommendations to better align regulatory labeling with scientific evidence, building on existing recommendations while addressing persistent gaps:

1. Provide prescribers/patients with contextual clarity on the magnitude of excess risks of ADRs and their clinical relevance. This should include the absolute excess risk, baseline risk,

seriousness, reversibility, preventability, level of causal evidence and certainty, and expected treatment benefit, expressed in patient-understandable terms such as absolute numbers over a defined time horizon.

2. Conduct mandatory periodic reviews with predefined and transparent criteria for de-listing unsupported ADR, particularly for currently rare spontaneous report ADRs. These criteria should include explicit evidence thresholds, such as the absence of excess risk in adequately powered randomized trials or individual-patient-data meta-analyses, the lack of consistent or reproducible disproportionality in pharmacovigilance studies, and confirmation by high-quality real-world pharmacoepidemiological studies. Structured real-world evidence (RWE) should be more systematically mobilized to quantify the causal strength of associations and the external validity of emerging ADR signals. When robust RWE refutes suspected causality, regulatory recommendations should enable proportionate label revision or de-listing. To preserve patient safety and limit the cost of false-negatives, particularly for rare, delayed, severe, or population-specific harms, de-listing should be accompanied by explicit safety measures, including continued active surveillance, periodic reassessment, predefined signal re-escalation criteria, and rapid label reinstatement if new convergent evidence emerges.⁴
3. Invest in mechanistic research to support causality assessment for ADRs. In this context, the recent characterization of the adenoviral inciting antigen and somatic hypermutation mechanism underlying COVID-19 vaccine-induced immune thrombotic thrombocytopenia,⁷ provided the biological plausibility necessary to strengthen causal inference and inform labeling decisions.
4. Integrate benefit information alongside safety information in patient-directed labeling. Because current patient-facing documents mainly emphasize indications, instructions for use, warnings, and adverse reactions, expected treatment benefits are often insufficiently

contextualized. For preventive therapies such as statins, ADR risk communication should therefore include clear, non-promotional, evidence-based information on individual and population-level benefits, including absolute cardiovascular risk reduction where available. Such benefit–risk proportionate communication could help patients and clinicians interpret uncertain or very low risks relative to the expected health gains of continued treatment.

In conclusion, the CTT analysis reaffirms the favorable safety profile of statins in randomized trials and challenges longstanding misconceptions regarding their safety. Its broader contribution should encourage regulators to communicate ADR risk and its inherent uncertainty in a proportionate and evidence-based manner. Precautions should remain central to pharmacovigilance. A proportionate approach, aligned with the strength of available evidence, is essential to maintaining trust, enhancing adherence, and optimizing population-level cardiovascular benefit.

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CONFLICT OF INTEREST

ML and JMD declared no competing interests. JD and PL declare no competing interests related to this work.

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