**THE MEANING OF THRESHOLDS**

The American College of Cardiology and the American Heart Association (ACC/AHA) 2019 guidelines on primary prevention of atherosclerotic cardiovascular disease (ASCVD) recommend different statin treatment regimens based on an estimate of ASCVD risk paired with therapeutic thresholds of 7.5% and 20% [1,2]. When grounding fairness analysis in threshold-based clinical guidelines, it is important to consider the assumptions underlying those thresholds, which can have implications for fairness.

The 7.5% treatment threshold for individuals without diabetes or clinical ASCVD and non-elevated LDL-C was established as a risk level above which net absolute benefit is positive. This was based on evidence from multiple RCTs, which studied the impact of statin treatment on ASCVD risk reduction [2] (Supplementary Section 7.3). The guidelines quantified net absolute benefit as a difference between benefits and harms, with *benefit* defined as as the number of patients who would need statin treatment to prevent one ASCVD event over 10 years (number needed to treat, NNT), and *harm* the number of statin-treated patients who would yield one excess case of diabetes over 10 years (number needed to treat to harm, NNH), both of which depend on 1) the estimate of a 10-year ASCVD risk of a patient, as well as 2) risk reduction from statin dose.

In 2013, The ACC/AHA committee [2] considered 5% and 7.5% as therapeutic thresholds. Those numbers corresponded to 10-year prevalence of ASCVD in the control groups of relevant primary prevention RCTs (Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TEXCAPS], Collaborative Atorvastatin Diabetes Study [CARDS], Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin [JUPITER], and Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese [MEGA]). The NNT and NNH for different statin doses were then compared at the thresholds. At 7.5%, NNH was higher than NNT for both moderate and high-intensity statin treatment - suggesting that treating patients with either dose would prevent more ASCVD events in more people than it would induce new cases of diabetes in. This observation led the committee to select 7.5% as an acceptable therapeutic threshold.

This threshold is not derived from an economic sense of utility, where the relative value of harms and benefits are accounted for. While the guidelines explicitly state that the harm of an ASCVD event is more significant than that of a new diabetes diagnosis, the relative weight of NNH and NNT is not quantified. If NNH and NNT were treated as equivalent, the optimal decision threshold would correspond to a risk value where NNH=NNT - and it would have been lower than 7.5% (~2.5% for moderate intensity statins, and ~6% for high intensity statins). The committee made their final recommendation based on the interpretation of the best available data and methods at the time. Therefore, the 7.5% threshold could be considered reflective of expert consensus rather than an algorithmic optimization.

The 20% threshold was added in the 2018 Cholesterol Clinical Practice Guidelines (Section 4.4.2) [1] as a risk value above which high-intensity statin therapy should be considered (with 7.5-20% range considered more appropriate for considering moderate- or high-intensity therapy). Further analysis of trial outcomes conveyed a relationship between proportional reduction in LDL cholesterol from baseline and reduction in ASCVD. Thus, a higher threshold was meant to convey the importance of higher intensity therapy to provide maximal benefit for high risk patients. This was enacted by introducing an additional decision threshold in the guidelines. Additionally, the 2019 Guidelines [5] included LDL-C reduction goals, rather than statin doses, for the different risk categories.

While we have heard anecdotal evidence in our conversations with physicians which implied that the thresholds were set to account for miscalibration, the guidelines imply that thresholds were not set explicitly to account for known miscalibration of the PCE models.

The guidelines also make several other assumptions, listed below, which are detailed in Table 5 of the Supplement to 2013 ACC/AHA guideline on the treatment of blood cholesterol [2].

- Similar relative risk reduction (RRR) for CVD events across patient groups.
- RRR is proportional to the degree of LDL-C lowering by statin therapy.
- Absolute benefit in risk reduction is proportional to baseline risk of group/individual and the intensity of statin therapy - patients and groups with higher absolute risk will get more absolute benefit from statins.
- Absolute risk for adverse outcomes is proportional to baseline risk of a given group, and the intensity of statin therapy.
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Since their publishing, some of those assumptions have been reevaluated [6].

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