REPLY: Origins and Previous Applications of Causal-Benefit Models

We thank Dr Dorresteijn and colleagues for their positive comments and constructive criticisms. We did omit a historical introduction.[1] We apologize. The causal-benefit model expresses quantitatively the simple principle that treatment should be based on the potential benefit of therapy balanced against the known risks of therapy. For the causal-benefit model to be applicable, there must be a pathophysiologically credible, calculable, continuous relation between the potency of the intervention in ameliorating the cause of a clinical event and the prevention of clinical events. In the case of statin therapy to prevent cardiovascular events, benefit can be calculated from the baseline risk of a clinical event, the baseline level of a cause of the event (apolipoprotein B [apoB] or low-density lipoprotein cholesterol [LDL-C]), and the anticipated effectiveness of treatment (reduction in apoB or LDL-C).[2] While conceptually aligned, our proposal goes beyond that of Glasziou and Irwig, who argued that the average results of a therapeutic trial do not apply to all patients within the trial and therefore, the features that identify increased risk identify those most likely to benefit from therapy.[3] However, our conceptual framework is identical in all essentials with that explicated by Soran, Schoefeld, and Durrington.[4]

Our article[1] had two principal objectives: first, to compare the advantages and disadvantages of the risk-factor model (which still remains the primary tool to select individuals for pharmacological primary prevention in all the major guidelines) with the advantages and disadvantages of the causal-benefit model. Second, to summarize the available analyses comparing the net benefit anticipated from application of the causal-benefit model versus the risk factor in the primary prevention of cardiovascular disease. Our focus was quantitative: number treated; number of events prevented. The results were consistent and compelling: more would be treated (of whom more would be younger and more would be women) and more events would be prevented, but at virtually the same number needed to treat, by applying the causal-benefit model rather than the risk-factor model.[1]

Dr Dorresteijn and colleagues identify several initiatives to extend beyond the boundaries of the 10-year risk-factor model in the 2021 European Society of Cardiology guidelines. We applaud these and we have also argued for a broader incorporation of a long-term benefit estimates. Moreover, better identification of younger individuals at higher risk of fatal and nonfatal major cardiovascular events remains of critical importance. The reality that more than 40% of atherosclerotic cardiovascular disease events occur in those under 65 continues to be underappreciated as does the fact that the majority of events in those over 65 are caused by atherosclerotic disease that appeared and progressed before 65.[1] In this context, more weight falls on how accurately and precisely the cause to be treated is measured. Thus, the 2019 European Society of Cardiology/European Atherosclerosis Society guideline acknowledgment of the superiority of apoB over LDL-C or non-high-density lipoprotein cholesterol as a more accurate marker of cardiovascular risk offers an important direction for broader implementation of apoB toward better preventative strategies.[5]

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