Step-wise Lipid-Lowering Therapy: Thinking Beyond the Guidelines

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This Commentary relates to the article by S. Deo et al on pages 120-128.

Once we accept our limits, we go beyond them
–Albert Einstein

Cardiovascular (CV) deaths have greatly overcome other causes of death worldwide. 1 Therefore, international scientific societies have boosted their efforts to curb detrimental CV risk factors. Yet, among many challenges, the clear and precise identification of high-risk patients, factoring in all risk factors, remains difficult, with international guidelines often proposing different criteria.

To date, a plethora of risk scores have been developed to identify patients at a higher risk of CV events and to better target available therapies. Coronary artery disease treated with coronary artery bypass graft (CABG) usually represents a self-evident high CV risk marker, both because it often involves complex multivessel disease and because it carries with it comorbidities at increased CV event risk, such as dyslipidemia. In the literature, it is henceforth well recognized that there is a beneficial effect of lipid-lowering therapy (LLT) on outcomes of CABG with recent or prior CABG.[2,3] In this panorama, lipid-related contribution to total CV risk is substantial, and aggressive control of cholesterol blood values, especially low-density lipoprotein (LDL) cholesterol, represents a milestone of secondary prevention.

Results of the IMPROVE-IT, FOURIER, and ODYSSEY trials,[4–6] epitomized in the slogan "the lower the better", drove the experts to further lower the LDL cholesterol cutoffs by escalation of LLT (including statins, ezetimibe, and PCSK9 inhibitors), which should be accomplished in the shortest possible time. None of the latest guidelines stemming from international societies included conversely treatment with bempedoic acid, since it was approved by regulatory agencies after their publication. However, investigating the long-term survival in the patients with CABG requires prolonged observational trials, whereas the use of computational algorithms is a useful and straightforward tool to project a putative outcome of a therapy in a very short time.

In this issue of the Journal, Deo et al simulated the reduction of LDL cholesterol from multistep escalation of LLT in 8948 very high-risk patients with CABG not at target, identified in accordance with the 2018 American Heart Association (AHA) guidelines,[7] by using a sophisticated Monte Carlo computerized model (Fig. 1). Interestingly, the authors predicted 2 scenarios, including or not bempedoic acid in the LLT escalation, and observed a projected median absolute 10-year risk reduction of 4.6% (interquartile range: 0.1%; 8.2%). It could be assumed that this result is trustworthy because the study was conducted on a wide patient sample, accurate data regarding baseline statin therapy and LDL cholesterol were available, and albeit it deals with a simulation, a strict methodological approach was followed. However, selection bias must be taken into account, considering that the enrolled

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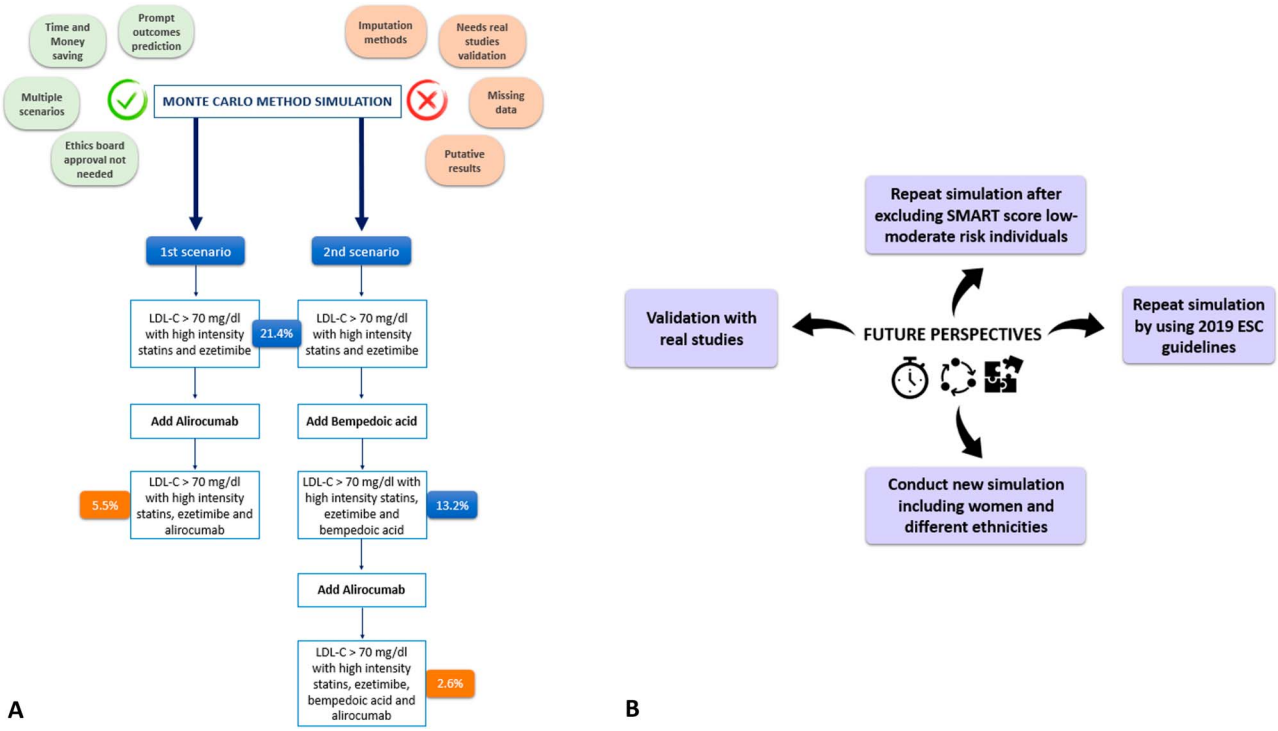

FIGURE 1. Main findings of the Monte Carlo simulation study on lipid-lowering therapy including alirocumab versus bempedoic acid (A) and its implications for future applications and investigations (B). ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; SMART, Secondary Manifestation of Arterial Disease.

individuals were mostly represented by White (74.3%) men, with women accounting for the 11.2% only. Indeed, gender and ethnicity underrepresentation issues are common in medical research and hereby may be easily explained by the fact that the study stemmed from the US Veteran Affairs health care system. Indeed, these results support previous works on high-intensity statin regimens or similarly potent LLT.[8,9]

Furthermore, Deo et al reported a significant reduction of alirocumab prescription when bempedoic acid is added to high-intensity statins and ezetimibe (21% vs. 13.2%), which is consistent with studies previously published.[10–13] Nevertheless, the number of patients who remained not within LDL cholesterol targets is halved (5.5% vs. 2.6%) by administering bempedoic acid with important implications on health care costs, since PCSK9 inhibitors cost twice more per year compared with bempedoic acid. In this regard, even if it might sound rough, this finding is worthy of mention because designing the correct line of a disease treatment might also include a cost-effective rationale.

Few other caveats should be considered as well. Although the presented results might seem conclusive, it should be stressed that after LLT, the median residual 10-year risk was 23.9% (16.7%–34.7%). Comparing these data with other works is challenging, as other studies investigating the same clinical setting are lacking. Notably, to better explore the reliability of results, the authors applied the SMART (Secondary Manifestation of Arterial Disease) score on the selected cohort, showing that almost 19% of individuals presented a low–moderate risk with consequent lower benefit from the LLT. On the contrary, patients at very high risk and extremely high risk according to the SMART score experienced a reduction of CV event recurrence 10-year risk from 56% to 34%. Indeed, the 2018 AHA guidelines were deemed to be unprecise in defying patients at real high risk of CV events recurrence.[14] It might thus be interesting to undertake a re-evaluation of results after excluding from the analysis the SMART score category at low–moderate risk, as well as conducting a projection of risk reduction in the subgroups (ie, diabetes, chronic kidney disease, and active smokers). Finally, to further widen the study findings, it would be desirable to project a similar LLT simulation on very high risk patients defined in accordance with the more stringent LDL cholesterol target recommended by the 2019 European Society of Cardiology guidelines and other experts (<55 mg/dL).[15,16]

In conclusion, the study conducted by Deo et al convincingly proves the efficacy of intensive LLT, especially when bempedoic acid is a part of the therapeutic combination, in patients undergoing CABG at very high risk of CV events recurrence. The paper embraces the timely need of using computational algorithms to promptly predict therapies efficacy and patients' outcomes, but it fatally pays the penalty of presenting a computerized model of CV prognosis, burdened by the use of imputation methods, rather than real-life follow-up. From this perspective, the current issue will stand as a brick in the wall until future studies will be performed to validate its results.

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