Monte Carlo simulations to meet the ESC recommended low-density lipoprotein cholesterol targets

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In the past decades the global burden of cardiovascular disease has nearly doubled (271 million - 1990 and 523 million - 2019) with corresponding increases in death and disability due to atherosclerotic cardiovascular disease (ASCVD).[1] Given the causal link between low-density lipoprotein cholesterol (LDL-C) and atherogenesis and the extreme LDL-C reduction achieved by proprotein convertase subtilsin/kexin type 9 inhibitors (PSCK9i), the European Society of Cardiology (ESC) 2019 statement recommended lowering LDL-C below 1.4 mmol/lit in very high-risk ASCVD patients.[2] Given these changes, prior studies have used Monte-Carlo simulations to investigate the ability of step-wise lipid lowering therapy (LLT) to reach these LDL-C targets in patients with prior myocardial infarction, or those receiving coronary artery bypass grafting.[3,4]

The present study by Brandts et al.[5] used data from the DA VINCI cohort, a prospectively collected multinational (19 European countries) pool of people with varying degrees of cardiovascular risk. Importantly, this patient group had an equitable proportion of people needing lipid lowering therapy for both primary (3000 patients) and secondary prevention (2888 patients) strategies. Furthermore, this is likely the first such analysis that also included a sizeable proportion of patients with peripheral arterial (PAD) (39%) and cerebrovascular disease (CeVD) (42%). Their aim of evaluating the projected benefit of stepwise LLT intensification was tested by running simulation models and calculating the proportion of patients meeting their LDL-C target at each step of this constructed pathway. They also used well-validated risk models to determine the potential clinical benefit that such LLT intensification may produce.

Their study presented the following key findings that can inform future decision-making. Firstly, at 10% the use of Ezetimibe, even for high-risk patients, was very low. Unfortunately, such dismal Ezetimibe utilization rates have been reported by other studies.[3] This is unfortunate as authors here reported that 60% (in primary prevention) and 42% (in secondary prevention) patients could reach their LDL-C target simply using a high-intensity statin + Ezetimibe combination. Ezetimibe resulted in 24% LDL-C reduction and a 6% relative risk reduction for major adverse cardiovascular events (MACE) in the IMPROVE IT trial.[6] Therefore, as ESC guidelines proposed, we should use this drug in combination with statins when possible. Secondly, this study also supported the observation that the aggressive 2019 ESC LDL-C target translates into a substantial proportion of very high-risk patients needing PCSK9i therapy[7]; even using the more conservative American Heart Association (AHA) criteria (<1.8 mmol/lit) we too reported similar findings.[3] Unfortunately, herein lies the Achilles heel of LLT as PCSK9i are expensive agents and the recent Swiss study reported a € 1700 per patient additional expenditure due to the widespread need for PCSK9i.[7] Patients in the US needing PCSK9i therapy already face high rates of pre-approval denial from their commercial insurance providers.[8] In the UK, a recent study reported that discounts of 30–50% were needed on Alirocumab (£ 4412) and Evolocumab (£ 4467) to achieve cost-effectiveness at the willingness-to-pay threshold of £ 30,000/QALY.[9] As discussed by the authors in the present study, limitations in reimbursement policies and pricing clearly preclude the wider real-world use of PCSK9i. Finally, authors reported a projected absolute risk reduction (ARR) of 7%, 9% and 8% respectively for patients with coronary artery disease (CAD), PAD and CeVD. This should encourage clinicians to aggressively promote LLT in this high-risk patient sub-population. A recent real-world study reported that the current uptake of PCSK9i among US Veterans with CeVD and PAD patients is quite low.[10]

The study had few aspects limiting widespread generalizability. Rather than real-world evidence, the data is from a developed cohort where the treatment compliance rates may be unduly high. The study did not examine using Bempedoic acid prior to PCSK9i therapy, drug that may become an important component of LLT in the future. In our study, we reported that adding Bempedoic acid after Ezetimibe led to a 10% reduction in the need for PCSK9i.[3]

In conclusion, this is an important study that further highlights the benefit of LLT intensification. It demonstrates that such a goal is possible with a stepwise approach but does underline the need for increasing the

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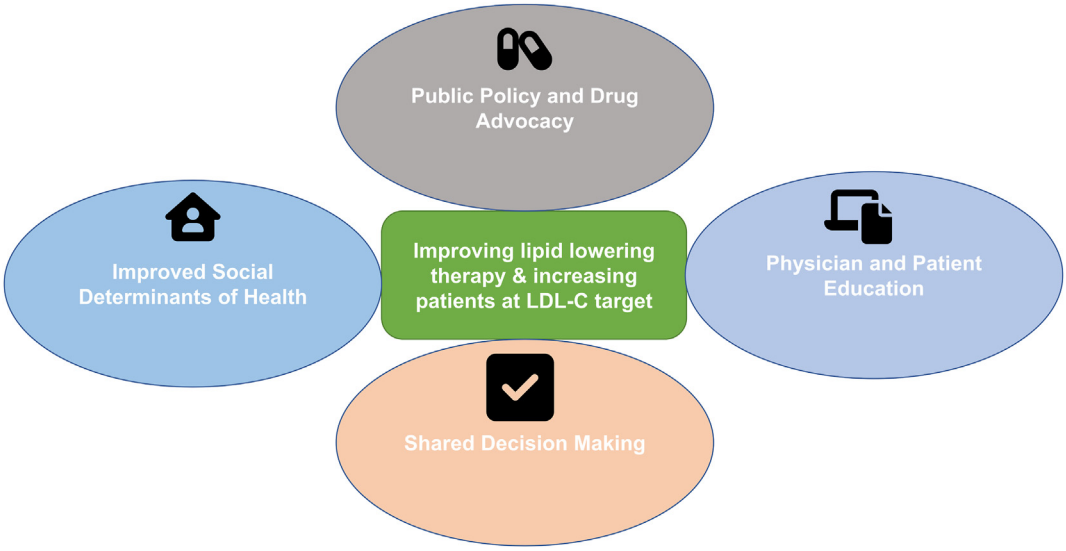

Fig. 1: Improving lipid lowering therapy and increasing the proportion of patients at LDL-C target needs a multi-pronged approach. Abbreviation: LDL-C, low density lipoprotein cholesterol.

use of PCSK9i therapy, especially in those patients at high-risk for recurrent events. The only way to achieve these goals is to adopt a multi-pronged approach of advocating for reduced drug costs, bettering the social determinants of health, increasing patient and physician education, and improving the shared decision-making process (Fig. 1).

Disclosure

I do not have any disclosures related to this manuscript.

Declaration of interests

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