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INVITED EDITORIAL

Cardiovascular risk assessment: are we getting all the information we need?

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This editorial refers to 'Comparison of the European and US guidelines for lipid-lowering therapy in primary prevention of cardiovascular disease' by B. Delabays et al., https://doi.org/10.1093/eurjpc/zwad193.

Lowering circulating low-density lipoprotein cholesterol (LDL-C) levels is one of the most effective approaches to preventing cardiovascular disease (CVD). Over the years, numerous guidelines have attempted to guide treatment and prevention by providing guidance on approaches to be implemented with the recommendation of LDL-C goals to be achieved. These recommendations are based on the assessment of individual CVD risk, estimated using various algorithms, such as the Pooled Cohort Equations (PCE) and the Systematic Coronary Risk Evaluation model (SCORE), which provide a calculation of the 10 year risk of a first atherosclerotic cardiovascular event. The most recent 2021 European Society of Cardiology (ESC) Guidelines on Cardiovascular Disease Prevention in Clinical Practice[1] introduced the use of SCORE2, an updated algorithm tailored to the European population that predicts the 10 year risk of the first onset of fatal and non-fatal cardiovascular (CV) event, overcoming some limitations of the previous SCORE, which only predicted the 10 year risk of CVD mortality and thus underestimated the overall CV risk.[2] This aspect is particularly relevant for younger people, among whom non-fatal cases are more prevalent.

In the study by Delabays and colleagues, published in this issue of *Eur J Prev Cardiol*, the authors compared therapy eligibility and predictive power using criteria from several European and US guidelines, including the 2016 and 2021 ESC, the 2019 American Heart Association/American College of Cardiology (AHA/ACC), and the 2022 U.S. Preventive Services Task Force (USPSTF) guidelines.[3] The population included in this analysis consisted of individuals without ASCVD who were not taking lipid-lowering therapy at baseline and had a mean age of 56.1 years; this population was followed for a median of 9 years.[3] When the individuals were grouped into risk categories according to the different guidelines, significant differences in eligibility for therapy were observed. First, when comparing the 2016 and 2021 ESC guidelines, fewer people would be recommended for therapy, while the percentage of those for whom the treatment may be considered remains almost unchanged. Second, the 2019 AHA/ACC and 2022 USPSTF guidelines show similar percentages of recommended treatment, which were higher than the 2021 ESC.[3] However, the percentage of people who were not eligible for treatment was significantly higher. When analysed by gender, significant differences were found between men and women. Overall, with all guidelines, women would have been less eligible for therapy and a lower percentage would have been recommended for therapy than men. Importantly, applying the 2021 ESC and the 2022 USPSTF guidelines resulted in a lower proportion of people eligible for lipid-lowering therapy, with approximately half of women who developed ASCVD during follow-up not eligible for therapy at baseline according to these two guidelines.[3] An important aspect that emerges from this analysis is that the 2021 ESC guidelines discriminate better against young people compared with other guidelines.

These findings can be viewed in two ways. On the one hand, they might suggest that overtreatment and potential adverse effects could be avoided by applying the latest guidelines. For example, a previous study showed that if the 2013 ACC/AHA guideline had been applied, 96.4% of men and 65.8% of women would have been eligible for a treatment recommendation.[4] On the other hand, this could also suggest that the categorization of CV risk by SCORE2 or PCE does not take into account the actual burden of prolonged exposure to elevated causal risk factors, such as LDL-C. In other words, an elevated LDL-C measured at a single time point cannot distinguish between a persistently elevated LDL-C and a rapidly rising LDL-C, two conditions that can have different effects.

Taking LDL-C as an example of causal risk factor (but our contention also applies to blood pressure), numerous studies have shown that exposure to elevated LDL-C levels cumulatively increases CV risk and that a higher cumulative LDL-C burden in early adulthood may be more strongly associated with CVD risk than a cumulative burden in later adulthood.[5,6] Indeed, an analysis of data from 4 large cohort studies consisting of 18 288 individuals showed that higher cumulative LDL-C burden and higher time-weighted average LDL-C levels during young adulthood and middle age were associated with an increased risk of incident coronary heart disease events, independent of midlife LDL-C levels.[7] This observation is confirmed by other studies showing that cumulative exposure to elevated LDL-C levels in young adulthood is associated with higher CV risk later in life.[5,8] These observations have introduced the key notion of a theoretical 'threshold' for LDL-C exposure beyond which coronary heart disease events are more likely to occur. Such a threshold has been empirically established at 8000 mg/dL-years and can be reached at different ages depending on LDL-C levels.[9] This implies that lower LDL-C levels over time delay the reaching of such a threshold.

As also discussed by the authors, a long-term benefit approach might be preferable to a risk approach, especially in young people. This approach implies that even in healthy people, preventive measures taken

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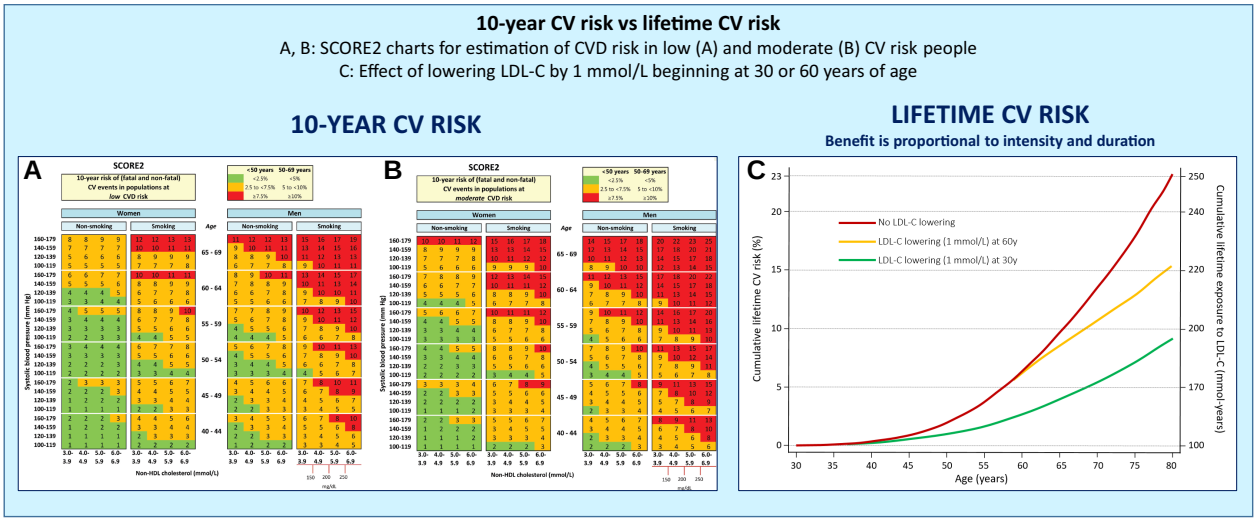

Central Illustration

early in life can help reduce the cumulative LDL-C burden and lower the CV risk later in life. This view is supported by the Mendelian randomization studies, which have shown that a relatively small, lifelong reduction in LDL-C levels results in greater predicted clinical benefit than a larger reduction achieved later in life, suggesting that 'the earlier the better'. How can this goal be achieved? The HOPE-3 trial proved that long-term statin treatment is useful for primary prevention in people without cardiovascular disease.[10] However, this does not mean that pharmacological interventions are absolutely necessary. We need to emphasize that lifestyle interventions are always recommended in the guidelines for all risk categories. While it is clear that lifestyle intervention cannot substantially lower LDL-C levels, it is also evident that small early reductions can provide a greater clinical benefit later in life. Ference and colleagues have shown that a person with a baseline LDL-C of 3 mmol/L can achieve approximately the same percent risk reduction by reducing LDL-C by 0.5 mmol/L for 40 years or by 1.5 mmol/L for 5 years.[11]

Having said that, is the assessment of the 10 year CV risk still a reliable estimate to determine the actual individual CV risk? Or do we need to consider the cumulative burden of LDL-C or blood pressure as the most important factor for intervention?

Based on a 10 year perspective, older people are bound to be at high or very high risk, as age is a major risk factor for ASCVD. On the other hand, this approach may not capture the future CV risk of younger people. In addition, we need to consider that the vast majority of the general population is in primary prevention, and therefore, although they have a lower CV risk compared with people in secondary prevention, they may contribute with a large number of events. Thus, a two-sided scenario can be outlined. We can continue to take care of people who have a high 10 year CV risk and treat them aggressively with the pharmacological armamentarium available so far. In this way, as people get older, they will have a higher and higher CV risk, largely due to age (which recapitulates the time of exposure to the causal risk factors). To reduce the CV risk in these people, a drastic reduction of the levels of the causal risk factors is required. Alternatively, or possibly simultaneously, attention can be focused on the general population (without neglecting the high-risk elderly) by attempting to reduce the cumulative effect of LDL-C and/or other factors such as hypertension through early approaches, thereby reducing the CV risk in later life. Whether this can be achieved through lifestyle interventions or pharmacological approaches capable of producing relatively small reductions in LDL-C levels very early in life remains to be fully explored.

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