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VIEWPOINT
Epidemiology and prevention

Combination lipid-lowering therapy as first-line strategy in very high-risk patients

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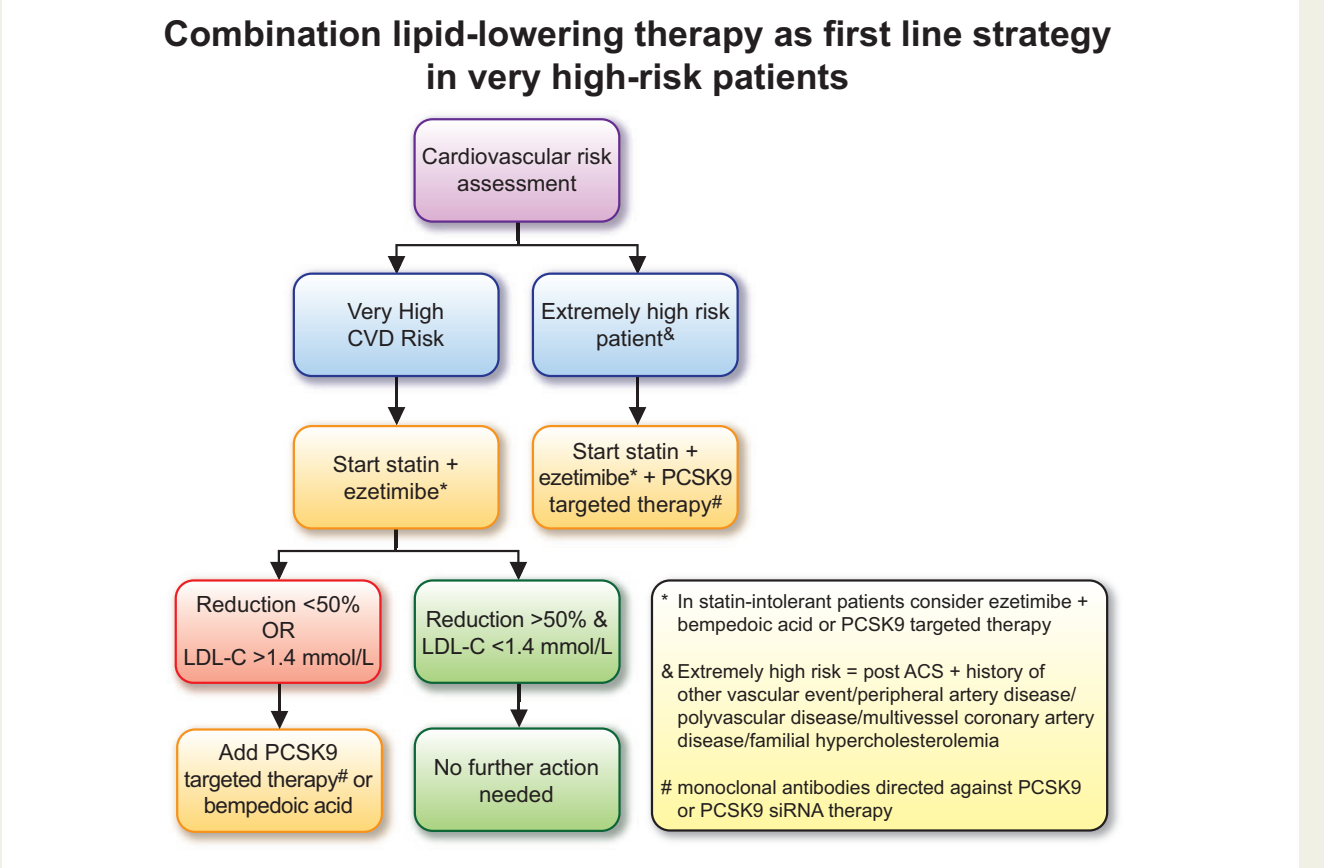

Graphical Abstract Combination lipid-lowering therapy as first line strategy in very high-risk patients.

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The proven case for low-density lipoprotein cholesterol lowering

When diet and lifestyle are insufficient to attenuate the risk of atherosclerotic cardiovascular disease, pharmacotherapy is mandated. A global approach that addresses multiple risk factors is required, including control of blood pressure and low-density lipoprotein (LDL) cholesterol. Statins have long been the first option for LDL cholesterol reduction. However, randomized clinical trials evaluating statins, and combination of statins with ezetimibe or PCSK9 monoclonal antibodies, have shown that what matters most is how much, when, and for how long the LDL cholesterol reduction is achieved rather than how it is achieved.[1,2] Meta-analyses of randomized clinical trials show that that 1 mmol/L reduction in LDL cholesterol reduces cardiovacsular risk by 21%.[1] This observation is further substantiated by Mendelian randomization studies that show that individuals with mutations in genes encoding the targets of lipid-lowering therapies had lower LDL cholesterol and a lower risk of cardiovascular disease.[1,3,4] Importantly, these genetic validation studies show a greater risk reduction (50–55%) per 1 mmol/L lowering, attributed to the cumulative lifelong reduction in LDL cholesterol exposure. Hence, the causality of LDL cholesterol has been proven beyond reasonable doubt and LDL cholesterol lowering has become the cornerstone of atherosclerotic cardiovascular disease prevention.[1–4]

Findings that lower LDL cholesterol levels are better with no evidence of harm have translated into recommendations for further lowering LDL cholesterol levels for three out of the four risk categories in the 2019 ESC/EAS guidelines on the management of dyslipidaemias.[5] For very high-risk patients, LDL cholesterol target goals were lowered from 1.8 mmol/L (70 mg/dL) to 1.4 mmol/L (55 mg/dL) in addition to the goal of achieving a 50% reduction from baseline, with very high risk being defined as documented atherosclerotic cardiovascular disease, or very high-risk prevention defined as diabetes mellitus with target organ damage or ≥3 major risk factors or early onset of type 1 diabetes mellitus of long duration, severe chronic kidney disease, a calculated SCORE ≥10% for 10-year risk of cardiovascular death, familial hypercholesterolaemia with one risk factor.[5] As absolute benefit depends upon both baseline risk and the absolute reduction in LDL cholesterol, the rationale for lower goals is that these patients have substantial risk which can be mitigated through more intensive LDL cholesterol lowering.[6]

The gap between low-density lipoprotein cholesterol guideline goals and current practice

Despite the steadily expanding armamentarium of LDL cholesterol-lowering therapies, there is still a big gap between guideline-recommended LDL cholesterol goals and what is achieved in real-world practice. In the DA VINCI study, it was shown that across Europe the majority of patients with atherosclerotic cardiovascular disease received moderate-intensity statin monotherapy (43.5%) or high-intensity statin monotherapy (37.5%). Only 9% of patients were on a combination of a statin with ezetimibe and 1% on a combination including a PCSK9 monoclonal antibody.[7] Unsurprisingly, achievement of the 2019 guideline-recommended LDL cholesterol goal of 1.4 mmol/L in these very high-risk patients was poor: 22% for patients receiving high-intensity statin monotherapy and 21% for patients receiving statins with ezetimibe vs. 58% for patients on a combination of PCKS9i with oral therapy. Data from registries such as this reflect 'best-case scenarios', as these reflect practice within clinics with a specialized interest. Thus, it is likely that real-world data are significantly worse regarding the proportion of patients achieving the LDL cholesterol goal. Indeed, two analyses, one from a prescription database in Germany and one from real-world clinical data in Poland, showed that only 20% of very high-risk patients achieved the previous LDL cholesterol target goal of <1.8 mmol/L recommended in the 2016 guidelines.[8,9]

The reasons behind the failure to achieve guideline recommendations are multiple. These include for example perceived side effects, lack of patient education, prescription of complex regimens, availability of drugs, and lack of reimbursement, all of which can lead to lower patient adherence.[10] Moreover, provider-related[11] as well as system-related barriers all negatively impact adherence.[10,11]

These barriers should be overcome as achieving guideline-recommended goals is important. A recent study compared two different treatment goals (2.6 and 1.8 mmol/L) in patients receiving lipid-lowering therapy as secondary prevention after an ischaemic stroke.[12] In the group of patients achieving the lower treatment goal, 8.5% of patients experienced a major cardiovascular event after a median of 3.5 years follow-up, compared to 10.9% in the group achieving the higher goal. This difference reflects a 22% lower risk for an achieved difference in mean LDL cholesterol levels between groups of 0.8 mmol/L, reinforcing the notion that for very high-risk patients, attainment of lower LDL cholesterol levels and indeed lower treatment goals provide meaningful risk reduction.

This line of reasoning can be extended to the results of the DA VINCI study. In this registry, 2974 patients with atherosclerotic cardiovascular disease were included, with 82% of these patients having a 10-year risk of fatal and non-fatal cardiovascular events of >20% according to the REACH algorithm.[13] The average LDL cholesterol level of this secondary prevention group was 2.1 mmol/L. An LDL cholesterol lowering from 2.1 to the guideline-recommended 1.4 mmol/L in this very high-risk group would result in a 14.7% relative risk reduction, according to a proportionally 21% risk reduction associated with 1 mmol/L lower LDL cholesterol. When assuming an average absolute cardiovascular risk of 20% or 40%, attaining LDL cholesterol levels of 1.4 mmol/L would translate into, respectively, 2.9 and 5.9 preventable CV events per 1000 persons per year. According to the results of observational and mendelian randomization studies, the achieved benefit could be potentially greater if treatment duration is increased beyond the duration of the original randomized controlled trials.

Intensive lipid-lowering combination therapy as first line

An extensive armamentarium of LDL cholesterol-lowering therapies is available, but implementation remains a challenge, requiring research into new strategies in patient care, including improvements in adherence, health literacy, and persistence of therapies, to ensure

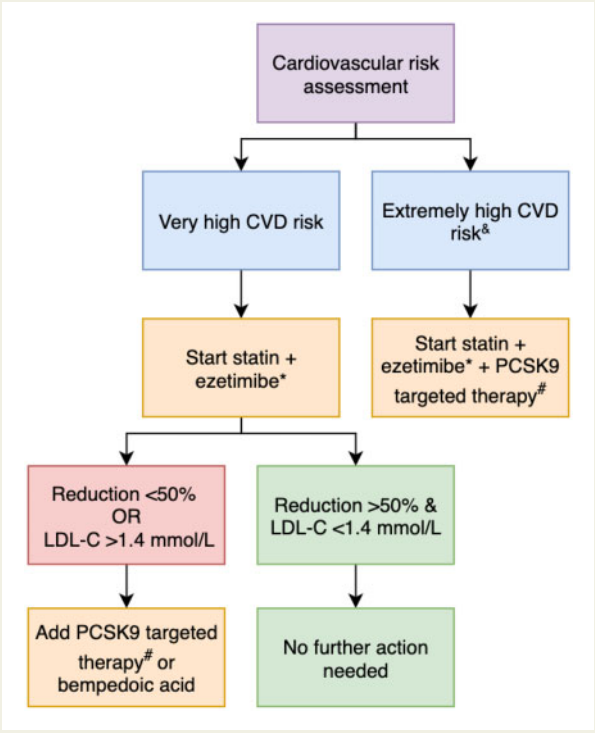

Figure 1 Simplified treatment algorithm for very high-risk patients with atherosclerotic cardiovascular disease. *Combination therapy = intensive statin therapy + ezetimibe. In statin-intolerant patients consider ezetimibe + bempedoic acid or ezetimibe + PCSK9 targeted therapy. &Extremely high-risk patient defined as having one of the following characteristics: post-acute coronary syndrome and a history of another vascular event in last 2 years; post-acute coronary syndrome and presence of peripheral artery disease or polyvascular disease; post-acute coronary syndrome and coexistent multivessel coronary artery disease; and post-acute coronary syndrome and familial hypercholesterolaemia.[15] #PCSK9 targeted therapy = monoclonal antibodies directed against PCSK9 (alirocumab or evolocumab) or PCSK9 siRNA therapy (inclisiran). The availability of bempedoic acid and PCSK9 siRNA therapy may vary between countries.

that a higher proportion of patients reach their LDL cholesterol goals.

As outlined above, statin monotherapy, even high-intensity statin monotherapy, will not be sufficient in the majority of patients to achieve guideline-recommended goals. Given the observation that the achieved cardiovascular benefit is independent of the mechanism by which LDL cholesterol is lowered, offers an opportunity to close the gap between guideline-recommended and achieved LDL cholesterol goals observed in daily practice. This, however, necessitates a sea change in practice and pragmatic thinking. We therefore propose to shift the paradigm for very high-risk patients from 'an intensive statin therapy first' approach to an 'intensive lipid-lowering therapy' approach. This implies that LDL cholesterol should be lowered in very high-risk patients, efficiently, pragmatically, and without delays.

Trials of lipid-lowering therapy over the past decade have resulted in precise quantification of the expected average reduction in LDL cholesterol for a given therapy (Supplementary material online, *Table S1*). This allows us to reliably predict control of LDL cholesterol through a simplified treatment algorithm for very high-risk patients (*Figure 1*). The first step of such a regimen for very high-risk patients is to start with a combination of statin therapy plus ezetimibe to achieve a large reduction of >50% in LDL cholesterol early as a practical standard of care. If patients do not achieve the 2019 guideline-recommended LDL cholesterol goal of >50% reduction and levels <1.4 mmol/L, a third lipid-lowering therapy, such as bempedoic acid or PCSK9 targeted therapies (either monoclonal antibodies against PCSK9 or PCSK9 siRNA), should be added. In patients who are statin intolerant, the first step of therapy regime should also be combination therapy, for example ezetimibe and bempedoic acid or ezetimibe and PCSK9-targeted therapy. In agreement with data from anti-hypertensive treatments, fixed-dose combination tablets lower LDL cholesterol more efficiently compared to two separate tablets and could therefore be considered.[14] For extremely high-risk patients, direct initiation of triple therapy should be considered prior to discharge from hospital in case of an acute event (for instance recurrent event within 2 years). As the relative benefit of additional LDL cholesterol reduction is half in the first year of treatment, compared with latter years, logically, greater absolute LDL cholesterol lowering is required to achieve greater relative cardiovascular benefits in the first year after a myocardial infarction. Moreover, if based on baseline and target LDL cholesterol a reduction of >80% is needed, addition of PCSK9 targeted therapy without delay is preferable, since it is unlikely that this will be achieved with statins and ezetimibe alone.

In conclusion, advances in the armamentarium of LDL cholesterol-lowering therapies enable physicians to achieve LDL cholesterol goals in very high-risk patients without restriction to a specific drug class. Indeed, LDL cholesterol lowering *per se*, and not the drug target resulting in LDL cholesterol lowering, is the main driver of cardiovascular risk reduction. Therefore, we should move away from 'high-intensity statin treatment' and 'the wait and watch paradigm' and instead start treating all very high- and extremely high-risk patients with combination therapy as the basic standard of care. This may afford significant improvements in population health across Europe.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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