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Reducing the risk of heart attack: the key role of lipid profiling and atherosclerosis imaging

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Despite major improvements in primary and secondary prevention, a flattening in the improvement of survival curves of patients with or at risk of acute myocardial infarction has been reached in recent years. Pharmacological therapies that reduce LDL cholesterol (LDL-C) levels have shown incremental clinical and vascular benefits according to the achieved LDL-C levels. However, a non-negligible rate of events still occurs in patients achieving very low LDL-C levels. In addition to risk factors related to inflammatory pathways, emerging lipid-related factors seem to account for this residual atherothrombotic burden, with accumulative evidence establishing lipoprotein (a) (Lp(a)) as the single greatest emerging risk factor. Ongoing trials will evaluate whether the pharmacological reduction of Lp(a) levels reduces the incidence of cardiac events, and therefore may represent a novel therapeutic target. In addition, implementing atherosclerosis imaging may help improve traditional clinical scores to identify better patients at high risk of cardiovascular events who may benefit more from early and effective treatment strategies. In the era of tailored medicine, direct imaging of atherosclerosis can play a crucial role in helping clinicians better stratify patient risk and patients better understand the burden of their disease, ultimately improving medication adherence and goal attainment.

Introduction

Atherosclerotic coronary artery disease still represents the first individual cause of morbidity and mortality worldwide, with its deadliest manifestation being acute myocardial infarction (MI). Over the past decades, several efforts have been made to improve risk stratification and reduce the occurrence of acute MI in both primary and secondary prevention. However, a flattening in the survival curves improvement has been reached and a not negligible rate of events still occurs in patients with or at risk of acute MI.[1–3]

Is LDL-C lowering still the primary goal?

With a large body of evidence demonstrating its effectiveness in preventing cardiovascular events, LDL-C is still reportedly the most effective strategy for lowering the risk of acute myocardial infarction (AMI). Long acknowledged as a major modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD), LDL-C has been shown in multiple clinical trials to significantly reduce the incidence of major adverse cardiovascular events (MACE), including acute MI, when effectively

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lowered. A substantial amount of research, including trials on statins and more recent agents such pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, supports these findings.

The ground-breaking Heart Protection Study (HPS) was among the first study to demonstrate a significant reduction in non-fatal MI and coronary death by ~25% with statin therapy.[4-6]

Subsequently, the development of more potent lipid-lowering agents, such as PCSK9 inhibitors, has brought new pharmacological opportunities in patients with atherosclerotic coronary artery disease. Large-scale trials such ODYSSEY Outcomes (PCSK9 inhibitor alirocumab) and FOURIER (PCSK9 inhibitor evolocumab) consistently showed that a highly intensive LDL-C lowering with PCSK9 inhibition reduces cardiovascular events, including acute MI. In FOURIER, the incidence of AMI was consistently lower in evolocumab-treated patients who had on-treatment LDL-C values of over 30 mg/dL than in controls (3.4 vs. 4.6%, $P < 0.001$).[7-10]

In parallel with clinical studies, imaging trials have robustly contributed to broadening the current understanding of the vascular effects of intensive LDL-C lowering therapies.[11-16]

Collectively, this accumulating evidence corroborates the notion that aggressive LDL-C lowering remains a cornerstone of preventing heart attacks and minimizing cardiovascular risk.

Secondary lipid-related goals: lipoprotein (a), hope, or hype?

When looking at survival curves of recent randomized trials on cardiovascular prevention it appears clear that a non-negligible rate of events still occurs in patients achieving very low on-treatment LDL-C levels.[2,7,17-20]

Thus, the interest in lipoprotein (a) (Lp(a)) as a new therapeutic target is growing. A Mendelian randomization analysis estimated a required Lp(a)-lowering effect size of 65.7 mg/dL to reach the same effect as a 38.67 mg/dL lowering of LDL-C.[21] In a recent analysis of the ODYSSEY OUTCOMES trial, Lp(a) lowering Lp(a) by alirocumab was an independent contributor to MACE reduction, suggesting that Lp(a) can be an independent treatment target after acute coronary syndrome.[22] Additionally, patients receiving PCSK9 inhibitors after AMI showed less significant lipid plaque regression in the presence of elevated baseline Lp(a) levels.[23] Accordingly, a growing body of evidence is testing the clinical value of selective targeting Lp(a). Previous large trials have already demonstrated the safety and efficacy of antisense oligonucleotides in potently reducing Lp(a) levels.[24,25] Similarly, in the OCEAN[a]-DOSE trial, Olpasiran (siRNA molecule that disrupts expression of Lp(a), degrading apolipoprotein(a) mRNA) reduced the Lp(a) concentration by more than 95% compared with placebo, with nearly all patients who received Olpasiran having a Lp(a) concentration of <125 nmol per litre.[26] Although no randomized placebo-controlled studies on outcomes are available to date, large studies are underway to demonstrate the prognostic impact of *ad hoc* reduction of Lp(a) levels. The ongoing Phase 3 HORIZON trial (Novartis Pharmaceuticals 2024; NCT04023552) will assess the impact of Lp(a) lowering with Pelacarsen—a liver-targeted antisense oligonucleotide that potently lowers Lp(a)—on major cardiovascular events in patients with established cardiovascular disease and baseline Lp(a) levels of at least 70 mg/dL (ClinicalTrials.gov ID NCT04023552).

The importance of imaging atherosclerosis in primary and secondary prevention

Accurate assessment of cardiovascular risk is a key to sustainable cost-effective strategies aimed at improving the quality of life and survival of the general population. The latest 2021 cardiovascular prevention guidelines recommend the use of the Systematic Coronary Risk Estimation 2 (SCORE-2) to estimate the 10-year risk of fatal and non-fatal cardiovascular diseases.[3,27-30]

Conclusions

In the current era, primary and secondary prevention of the deadliest event of coronary artery disease, namely acute MI, are still far from optimal in the general population. Lowering LDL-C levels is mandatory to substantially reduce risks according to the patient individual risk. However, although the desired level of LDL-c is reached, some patients still have a considerable cardiovascular residual risk linked to other elements, particularly Lp(a) levels. Ongoing trials will evaluate whether the reduction of Lp(a) levels reduces the incidence of cardiac events, and therefore represent a novel therapeutic target. Lastly, imaging of coronary atherosclerosis is warranted to ultimately improve preventive strategies and patient prognosis by directly visualizing the atherosclerotic burden and composition.

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Data availability

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