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Review article

Role of dual lipid-lowering therapy in coronary atherosclerosis regression: Evidence from recent studies

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ABSTRACT

Despite recent therapeutic advances, there is an unmet need in cardiovascular disease prevention. Clinical trials and meta-analyses have established that LDL-C lowering, particularly by statin therapy, reduces the progression of coronary atherosclerosis and the risk of coronary events. Insufficient LDL-C reduction and high residual risk in a significant proportion of statin-treated patients signify that additional therapies are required to deliver more effective coronary care. Pharmacological inhibition of cholesterol absorption (with ezetimibe) and PCSK9 activity (with evolocumab or alirocumab) provides potentially useful approaches for the therapeutic modulation of LDL-C metabolism in statin-treated patients. In recent trials, combination strategies involving a statin and non-statin agent (ezetimibe or evolocumab) have been shown to promote coronary atherosclerosis regression and improve cardiovascular outcomes in patients with moderate-to-high cardiovascular risk. This review summarizes recent evidence on the effects of dual lipid-lowering therapy on coronary atherosclerosis.

1. Introduction

Over the past few decades, mortality rates for patients with coronary artery disease (CAD) and myocardial infarction have dramatically decreased thanks to advances in pharmacologic and interventional treatments [1]. Numerous clinical trials have established the importance of lipid-lowering therapy in primary and secondary prevention and highlighted the role of statins, which inhibit cholesterol synthesis and increase the clearance of low-density lipoprotein cholesterol (LDL-C) [2,3], as first-line agents in patients with cardiovascular disease [4,5]. LDL-C is a causal factor in the pathophysiology of atherosclerotic heart disease [6], and coronary plaque regression has a significant positive correlation with LDL-C and non-high-density-lipoprotein cholesterol (non-HDL-C) reduction [7,8]. High-intensity statin therapy has been demonstrated to reduce LDL-C [4,6] and promote coronary atheroma stabilization [9] and regression [4,9–11] in patients with acute coronary events [7,10] or stable coronary disease [4]. In virtual-histology (VH) study, statin treatment was also associated with changes in atheroma composition, reducing fibro-fatty components and increasing dense calcium volume [12]. However, despite high-intensity statin therapy atherosclerosis continue to progress in up to one-third of patients [13], and there is an unmet need in lipid pharmacotherapy to reduce the "residual risk" of coronary events [14]. Therefore, a multi-target pharmacological approach is often required to further lower LDL-C levels, diminish the atherosclerotic burden, and improve outcomes, especially in high-risk patients [6]. In the past twenty years, dual antiplatelet therapy has shown a net benefit over single antiplatelet therapy in selected high-risk CAD patients (e.g., those with a recent acute coronary syndrome or stent implantation) [15,16]. Similarly, in the past few years, dual lipid-lowering therapy, which combines a statin with a second drug having a different mechanism of action, has been shown to

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CuVIC, Effect of Cholesterol Absorption Inhibitor Usage on Target Vessel Dysfunction After Coronary Stenting; DAPT, dual antiplatelet therapy; DEBATE, Drugs and Evidence-Based Medicine in the Elderly; DULT, dual lipid-lowering therapy; GLAGOV, Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound; IMPROVE-IT, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PAV, percent atheroma volume; PCI, percutaneous coronary intervention; PRECISE-IVUS, Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound; REVEAL, Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification; SAP, stable angina pectoris; TAV, total atheroma volume.

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effectively counteract atherosclerosis progression and improve cardiovascular outcomes by the LDL-C pathway blockade [17,18]. In patients with CAD and treated with statins, coronary atherosclerosis regression has been associated with a significant clinical benefit, whereas disease progression is related to a worse outcome [19]. Therefore, examining coronary atherosclerosis development is generally considered useful in the assessment of cardiovascular protection in clinical trials, as a surrogate marker of the outcomes in CAD patients [9,20].

This review summarizes recent evidence on the effects of dual lipid-lowering therapy on coronary atherosclerosis regression.

2. Dual lipid-lowering therapy: role in atherosclerosis regression

Until a few years ago, despite the extensive evidence showing that statin therapy slowed the progression and induced regression of coronary atherosclerosis [4,5,9,11], it remained unclear whether plaque progression was additionally slowed by a further reduction in LDL-C levels achieved using combination (dual) lipid-lowering therapy (statin plus a non-statin agent). This issue was investigated by two recent clinical trials in CAD patients, evaluating the anti-atherosclerotic effect of ezetimibe [17] and evolocumab [18] by intravascular ultrasound (IVUS). IVUS is a catheter-based imaging modality that generates high-resolution imaging of the coronary wall, allowing the measurement of changes in the atherosclerotic plaque volume in anatomically matched arterial segments in serial studies [21].

2.1. Ezetimibe: cholesterol absorption inhibition and atherosclerosis regression

Ezetimibe blocks the Niemann-pick C1-like 1 protein (NPC1L1), a cholesterol transporter primarily expressed in the small intestine and involved in the absorption of both biliary and dietary cholesterol [22]. Pharmacological inhibition of NPC1L1 by ezetimibe reduces cholesterol absorption and, consequently, lowers serum LDL-C and non-HDL-C, in both mono- and combination therapies [23]. In conjunction therapy with a statin, blocking cholesterol absorption is useful to overcome the otherwise enhanced lipid absorption that occurs during the inhibition of cholesterol synthesis [22]. Indeed, enhanced intestinal cholesterol absorption represents a potential weak point in statin monotherapy, as it may increase the absorption of other atherogenic lipids, such as oxysterols, with a possible unfavorable impact on lipid and metabolic profiles [24,25], and cardiovascular outcome [24,26]. By inhibiting cholesterol absorption, ezetimibe exerts beneficial effects that are complementary to statin therapy: in the recent IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial), ezetimibe (10 mg) plus simvastatin (40 mg) significantly lowered LDL-C, non-HDL-C and triglyceride levels, and reduced the rate of cardiovascular events (absolute risk reduction of 2.0% points; hazard ratio, 0.936; 95% confidence interval, 0.89 to 0.99; $p = 0.016$, for the primary composite end point of death from cardiovascular causes, major coronary event, or nonfatal stroke) in patients with recent acute coronary syndrome (ACS), compared to simvastatin monotherapy [27].

2.1.1. The PRECISE-IVUS study

The Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound (PRECISE-IVUS) study, published in 2015, investigated the effects of ezetimibe plus atorvastatin on coronary atherosclerosis progression [17]. This multicenter, prospective, randomized, controlled, assessor-blind study compared atorvastatin monotherapy to atorvastatin plus ezetimibe in patients with CAD, either ACS or stable angina pectoris (SAP), and a baseline LDL-C level > 100 mg/dl. A total of 246 patients (mean age, 66 years; SD = 10 years) were enrolled after a coronary angiography procedure (with or without a percutaneous coronary intervention [PCI]). From the total population, 122 patients were randomized to receive atorvastatin plus ezetimibe (LZ group) and 124 to atorvastatin alone (L group). Ezetimibe was dosed at 10 mg/day while atorvastatin was up-titrated until a target LDL-C < 70 mg/dl was reached. IVUS was done to quantify coronary artery atheroma volume, expressed as percent atheroma volume (PAV) and total atheroma volume (TAV). The primary efficacy endpoint was the absolute change in PAV of the coronary target segment (a non-PCI site > 5 mm proximal or distal to the PCI site) from baseline to follow-up. Secondary endpoints included percent change in normalized TAV and variations in the lipid and metabolic profiles (e.g., LDL-C, triglyceride, HDL-C, apolipoprotein B, lipoprotein(a), lathosterol, cholestanol, sitosterol, and campesterol). Serial IVUS was performed in 100 patients in LZ group and 102 patients in L group. Baseline LDL-C levels were not significantly different between these groups (109.8 mg/dl in LZ group *vs.* 108.3 mg/dl in L group) and about half of these patients had ACS (51 in LZ group; 49 in L group). For the primary endpoint, atorvastatin plus ezetimibe combination therapy was non-inferior to atorvastatin alone, with a mean difference in absolute change in PAV between groups of −1.538% (95% confidence interval, −3.079%–0.003%). For superiority, the absolute change in PAV was significantly higher in LZ group than in L group (−1.4% *vs.* −0.3%; $p = 0.001$). Also, a significantly greater percentage of patients in LZ group had coronary plaque regression (78% *vs.* 58%; $p = 0.004$). Considering the secondary IVUS endpoint, percent change in normalized TAV was significantly higher with dual lipid-lowering therapy (LZ group) than with statin therapy alone (−6.6% *vs.* −1.4%; $p < 0.001$), with a greater proportion of patients with disease regression (75% *vs.* 58%; $p = 0.02$). Moreover, when the analysis was performed separately according to the patients' clinical presentation (ACS *vs.* SAP), the effect of combination therapy on plaque regression appeared even more favorable in the ACS cohort than in the SAP cohort, regarding both absolute change in PAV (−2.3% in LZ group *vs.* −0.2% in L group; $p < 0.001$) and percent change in normalized TAV (−10.2% in LZ group *vs.* −1.3% in L group; $p < 0.001$). Conversely, in the SAP cohort, the differences in absolute change in PAV and in the percent change in normalized TAV between the two treatment groups were not statistically significant. Considering the secondary laboratory endpoints, LDL-C levels at 9–12 months were significantly lower in LZ group (mean, 63.2 mg/dl; SD = 16.3 mg/dl) than in L group (73.3 mg/dl; SD = 20.3 mg/dl; $p < 0.001$), with a greater proportion of patients reaching LDL-C levels < 70 mg/dl (72% *vs.* 47%, respectively; $p = 0.001$). LDL-C levels were significantly lower in plaque regressors (any negative change in PAV) than in plaque progressors (any positive change in PAV) (65.5 mg/dl *vs.* 74.3 mg/dl; $p = 0.003$). Moreover, cholesterol absorption markers (campesterol, sitosterol, campesterol-to-cholesterol ratio, sitosterol-to-cholesterol ratio, campesterol-to-lathosterol ratio and campesterol-to-cholesterol ratio) were all significantly lower in LZ group than L group. Finally, linear regression analysis showed a relationship between the absolute change in PAV and both LDL-C levels at follow-up and percent change in campesterol-to-cholesterol ratio, but the effects were more prominent in the ACS than SAP cohort. Both pharmacological strategies were found to be safe, with few adverse drug reactions or altered laboratory test results, and an identical rate of cardiovascular events (including target lesion/vessel revascularization) in the two groups.