Lipid-Lowering Therapy of Post-Acute Coronary Syndrome

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It has been consistently demonstrated that circulating lipids and particularly low-density lipoprotein cholesterol (LDL-C) play a significant role in the development of coronary artery disease (CAD). Several trials have been focused on the reduction of LDL-C values in order to interfere with atherothrombotic progression. Importantly, for patients who experience acute coronary syndrome (ACS), there is a 20% likelihood of cardiovascular (CV) event recurrence within the two years following the index event.

lipid-lowering therapy (LLT) post-acute-coronary-syndrome PCSK9 inhibitors

1. Introduction

Dyslipidemia is a metabolic disorder determined by the concurrence of genetic conditions and unhealthy lifestyles [1].

A close relationship between the incidence of atherosclerosis and serum cholesterol levels has been well recognized [2], and increased values of low-density lipoprotein cholesterol (LDL-C) are the primary cause of the development and progression of atherosclerosis [3].

Indeed inflammation, LDL-C, platelet activation, and endothelial dysfunction have been considered the leading atherogenic factors [4][5]. Remarkably, it has been shown that LDL-C and circulating monocyte levels are linked, confirming the correlation between lipids, inflammatory status, and CAD progression [6][7].

Furthermore, it has been established that intensive lipid-lowering therapy (LLT) may improve plaque phenotype, contributing to plaque stabilization [8][9].

Moreover, it has been claimed that an intensive LLT is correlated with better outcomes in those patients who experienced ACS [10][11].

Consequently, the reduction [10][12] of circulating LDL-C is one of the most relevant goals to achieve for CVD prevention. This goal is achievable thanks to several effective pharmacological interventions currently available [13].

Table 1 summarizes the action of LLT.

Table 1. Main lipid-lowering drugs.

Drug Classes	Mechanism of Action	Expected Proportional LDL-C Reduction (vs. Placebo)	Main RCTs after ACS
Statins (Moderate Intensity): Atorvastatin 10–20 mg; Rosuvastatin 5–10 mg; Simvastatin 20–40 mg, etc.	Inhibit the activity of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase	30% [14][15][16]	FLORIDA [17], PACT [18], A to Z [19]
Statins (High Intensity): Atorvastatin 40–80 mg; Rosuvastatin 20–40 mg		50% [14][15][16]	MIRACL [20], PROVE-IT TIMI 22 [10]
Ezetimibe	Inhibits the Niemann–Pick C1-like 1 transmembrane protein	20% [16]	
Bempedoic Acid	Inhibits adenosine triphosphate citrate lyase	15–25% [16]	CLEAR ACS [21] (ongoing)
PCSK9-i (Alirocumab, Evolocumab)	Monoclonal antibodies which selectively bind to extracellular PCSK9, preventing LDL-R degradation	60% [14][15][16]	EVOPACS [22], EPIC-STEMI [23], VCU-AlirocRT [24]
PCSK9 siRNA (Inclisiran)	Prevent the translation of PCSK9 messenger RNA	50% [16]	VICTORION-INCEPTION (ongoing)
Statin + Ezetimibe	Combined	Maximum 65% [14][15][16]	IMPROVE-IT [25]
Bempedoic Acid + Ezetimibe	Combined	35% [16]	
High Intensity Statin + PCSK9-i	Combined	75% [14][15][16]	
High Intensity Statin + Ezetimibe + PCSK9-i	Combined	85% [14][15][16]	

1.1. Statins

Statin therapy has been shown to decrease all-cause mortality and 5-year incidence of major adverse cardiovascular events (MACE) by 12% and 21%, respectively, per mmol/L LDL-C reduced (roughly equivalent to 39 mg/dL) [26]. A 20% reduction of CV adverse events rate has been reported using statins compared with placebo and high-intensity statins compared with low-intensity statins for each LDL 1.0-mmol/L reduction [12].

Nowadays, statins are considered the first-line pharmacological therapy in order to manage dyslipidemia and reduce CV risk [27]. Some statins derive from fungal fermentation, such as lovastatin, pravastatin, and simvastatin

[28], others from synthetic processes (atorvastatin, rosuvastatin) [28].

It has been shown that statins competitively inhibit the activity of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGR), which converts 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) into mevalonic acid, a cholesterol precursor [29].

This phase is an early rate-limiting step in cholesterol biosynthesis. The binding of statins with HMG-CoA reductase is reversible [30].

As a result of statin activity, a non-linear dose-dependent LDL-C reduction occurs.

Considering the fact that mevalonate, derived from HMGR, is also the precursor of many other nonsteroidal isoprenoid compounds, such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (FPD), statins also affect the Ras-related small GTPase signaling pathway (Ras and Rho) [31].

Some of the statins' pleiotropic effects are ascribed to the inhibition of these intracellular isoprenoid-dependent proteins [32]. Indeed, several cardioprotective effects of statins observed during chronic use have been thought to be not directly linked to cholesterol levels [33][34][35].

Anti-inflammatory activity has also been postulated [36]. A potent modulating effect on endothelial cell nitric oxide synthase (eNOS) resulting in the upregulation of eNOS enzyme and a decrease in nitric oxide (NO) production [36], as well as a reduction in cytokine C-reactive protein (CRP) levels, has been reported [20][37][38][39].

A large number of experimental and clinical studies investigated the potential additional effects of statins, postulating an improvement in endothelial function and vascular tone, plaque stabilization effects and anti-thrombotic activity, and reduction in oxidative stress [36].

An incremental lowering of LDL-C values, which has been shown in patients receiving intensive statin therapy compared with those treated with moderate-dose statins, results in a lower rate of nonfatal CV events [10][19][40][41][42]. Good tolerance has been generally reported in patients treated with statins, but 20% of intolerant patients reported statin intolerance syndrome with adverse effects on muscles, varying from myalgia to myopathy, myositis, and rhabdomyolysis [43][44]. Statin-induced intolerance may cause therapy interruption [45][46].

A rise in the risk of adverse CV outcomes has been reported in patients discontinuing statin therapy [47][48]. A genetic predisposition has been hypothesized to be involved in the development of statin-induced muscle failure [49].

However, safety issues associated with intensive statin therapy and the evidence of residual risk of recurrent CV events [50] have led to the introduction of additional non-statin therapies in clinical practice [51].

2. Ezetimibe

Ezetimibe joins a new drug class of selective cholesterol absorption inhibitors that block the internalization of cholesterol into enterocytes at the level of the brush border of the small intestine [52].

The ezetimibe-mediated inhibition of the Niemann–Pick C1-like 1 (NPC1L1) polytopic transmembrane protein results in reduced intestinal cholesterol absorption [53].

A 10–14% and 23–24% LDL-C plasma level reduction has been observed in patients treated with ezetimibe alone or in addition to statins, respectively [54][55]. Ezetimibe combined with a low dose of statins may represent a suitable option in case of symptoms of intolerance in patients treated with full doses of statins [54]. More recent studies have shown great results with ezetimibe and bempedoic acid co-therapy, with a 38% mean difference in LDL cholesterol level reduction compared to the placebo [56].

In the IMPROVE-IT trial, in high-risk patients post ACS, the combination strategy of ezetimibe 10 mg and simvastatin 40 mg proved to be superior to simvastatin 40 mg alone in lowering the recurrence of CV events, irrespective of baseline LDL-C levels [57]. An incremental beneficial effect of ezetimibe added to statin has been observed in patients with DM and in those without DM but at high risk of recurrent CV events [58].

3. Bempedoic Acid

Bempedoic acid has recently entered the pharmacological armamentarium for dyslipidemia treatment [59].

After its conversion to the active metabolite by acyl-CoA synthetase 1 (ACSVL1), exclusively expressed in liver cells, bempedoic acid lowers cholesterol synthesis by inhibiting adenosine triphosphate (ATP) citrate lyase, which, in the enzymatic cascade that leads to cholesterol synthesis, acts upstream of HMGCR.

Similarly to statins, reduced hepatic cholesterol synthesis induced by bempedoic acid leads to the upregulation of LDL-R expression and, consequently, reduction in LDL-C levels [60]. The reason why fewer muscular adverse effects have been associated with this therapy is that bempedoic acid is a prodrug selectively activated in the hepatic tissue. In skeletal muscle, the prodrug can not be activated due to the absence of ACSVL1, explaining the reduction in adverse muscle effects mentioned above. Moreover, ATP citrate lyase downregulation and AMP-activated protein kinase (AMPK) upregulation improves glucose metabolism regulation [49] and reduces the inflammatory pathway and cytokine production [61]

The safety and efficacy of the long-term use of bempedoic acid have been investigated in several clinical trials, including Cholesterol Lowering via BEmpedoic Acid, an ACL-inhibiting Regimen (CLEAR) Tranquility [56], CLEAR Serenity [62], CLEAR Wisdom [62], and CLEAR Harmony [63][64]. At a daily dose of 180 mg, an LDL-C reduction from 17.4 to 28.5% was obtained [65].

Recently, in a trial that included 13,970 patients, 69.9% with a previous CV event with statin intolerance, the incidence of primary endpoint events (death from CV causes, nonfatal myocardial infarction, nonfatal stroke, or

coronary revascularization) was 13% lower in the treated group. The incidences of gout and cholelithiasis were higher with bempedoic acid than with placebo (3.1% vs. 2.1% and 2.2% vs. 1.2%, respectively), as were the incidences of small increases in serum creatinine, uric acid, and hepatic enzyme levels [66].

4. PCSK9 Inhibitors

Proprotein convertase subtilisin-like kexin type 9 (PCSK9) is a serine protease mainly expressed in the liver that targets LDL-Rs, promoting their lysosomal degradation and decreasing circulating LDL-C clearance [67]. PCSK9 monoclonal antibodies (mAbs) selectively bind to extracellular PCSK9, preventing LDL-R degradation and lowering plasma LDL-C levels. Two fully human mAbs, Alirocumab and Evolocumab, have been approved by FDA and EMA [68].

Statin treatment increases circulating PCSK9 serum levels; consequently, the greatest effect of these mAbs has been observed when used in combination with statins [69]. A reduction in LDL-C plasma levels has been shown, of up to 65% for alirocumab and 80% for evolocumab, following an injection every 2 or 4 weeks [70].

PCSK9 mAbs were associated with a 20% lower risk of myocardial infarction, a 22% lower risk of ischemic stroke, and a 17% lower risk of coronary revascularization [71]. Their use was associated with a favorable safety profile without increasing risk of neurocognitive adverse events, liver enzyme elevations, rhabdomyolysis, or new-onset diabetes mellitus. According to the GLAGOV data [72], both molecules have been shown to favor morphological stabilization and reduction of carotid plaques [9][73][74][75][76], delaying ASCVD progression.

5. Inclisiran

Small interfering RNA (siRNA) molecules now represent the next generation of drugs designed to antagonize PCSK9. Inclisiran is an siRNA specific for PCSK9 that prevents the translation of PCSK9 messenger RNA, leading to decreased concentrations of the protein and lower concentrations of LDL cholesterol.

Inclisiran blocks the expression of a specific gene by selectively silencing the translation of PCSK9 messenger RNA (mRNA) [77], leading to a long-lasting reduction in LDL-C even up to 12 months [78][79]. It was thought that the reason why inclisiran has such long-term efficacy is that the silencing complex remained active even after mRNA degradation, resulting in a considerable and long-lasting reduction in plasma LDL-C levels [78]. Consequently, inclisiran has been considered an attractive therapeutic option, particularly for non-adherent patients [80]. What the impact of inclisiran on reducing lipoproteins and MACE is, has been largely investigated in the ORION/VICTORION studies [79][81][82][83][84][85][86][87][88][89][90][91][92][93][94][95], which evidenced a decrease in LDL-C over 1 year of 29.5–38.7% and 29.9–46.4% after a single dose and after two doses, respectively ($p < 0.001$). Moreover, Lp(a) has been shown to significantly decrease.

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