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Review Article

Current and future options in cholesterol lowering treatments

Avishay Elis [a,b]

[a] Department of Internal Medicine "C", Beilinson Hospital, Rabin Medical Center, Petah-Tikva, Israel
[b] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

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ABSTRACT

The relative risk reduction of cardiovascular events is proportional to the absolute reduction in LDL-C levels, the primary target of therapy, no matter the way of reduction. During the last decades, the therapeutic regimens for reducing the LDL-C levels have been immerged and improved, with favorable effects on the atherosclerotic process and clinical benefits of various cardiovascular outcomes.

From a practical view of point, this review is focusing only on the current available lipid lowering agents: statins, ezetimibe, anti PCSK9 monoclonal antibodies, the small interfering RNA (siRNA) agent, Inclisiran, and Bempedoic acid. The recent changes in lipid lowering regimens, including the early combination of lipid lowering agents and "Low LDL-C" levels <30 mg/dL for high/very high cardiovascular risk patients will also be discussed.

1. Introduction

Dyslipidemia is one of the major risk factors for cardiovascular disease (CVD), the main cause of death worldwide. There is extensive evidence that the low density lipoprotein (LDL) is the main causal agent in the athero-thrombotic process and the fundamental determinant of vascular risk. Furthermore, trials of LDL-C lowering indicate that the relative risk reduction of cardiovascular (CV) events is proportional to the absolute reduction in LDL-C levels, no matter the way of reduction, with no evidence of any lower LDL-C level threshold. As a consequence, LDL-C levels (or non - HDL-C in cases where it can't be calculated) became the primary target of therapy. The intensity of LDL-lowering therapy is based on: the patient's risk level (irrespective of the cause) and the baseline LDL-C levels. According the 2019 ESC/EAS guidelines, the LDL-C levels for high/very high CV risk subjects should be below 70 or 55 mg/dL, respectively with $\geq$ 50% reduction from baselines levels [1–4].

The treatment options for hypercholesterolemia have been immerged and improved during the last decades, with favorable effects on the atherosclerotic process and clinical benefits on various cardiovascular outcomes (CVO). All available agents affect the LDL receptor (LDL-R), the common pathway for reducing the LDL-C levels. Many other new lipid lowering modalities are under clinical investigation.

From a practical view of point, this review is focusing only on the current available lipid lowering agents.

2. Statins

Statins are the main agents used, and will be used, in the near future for controlling LDL-C levels. They reduce the intrahepatic production of cholesterol by competitively inhibiting the key enzyme, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, thereby limiting the conversion of HMG-CoA to mevalonic acid, the precursor of cholesterol. The reduction of hepatic cholesterol synthesis leads to overexpression of the LDL-R and consequently to increased uptake of LDL particles into the cells, resulting in a decrease in plasma cholesterol levels [5].

High dose potent statins reduce the LDL-C levels by up to 50% with favorable effects on the volume and stability of the atherosclerotic plaque. According to meta-analysis of 14 randomized trials, statin therapy leads to a decrease of up to 12% in all-cause mortality per mmol/L lowered LDL-C, as well as decrease in various CV outcomes [2].

The different statins have varying abilities to lower LDL-C (e.g.: simvastatin 10 mg, pravastatin 20 mg – 27%; simvastatin 40 mg, atorvastatin 20 mg – 40%; atotvastatin 80 mg, rosuvastatin 20 mg –54%) with maximal reductions of approximately 60% seen with rosuvastatin 40 mg. Doubling the dose of a statin results in only an approximate 6% further decrease in LDL-C levels. The percent reduction in LDL-C levels is similar in patients with high and low starting LDL-C levels, but the absolute decrease is greater if the starting LDL-C is high. Statins are also very effective in lowering non-HDL-C levels, as well as lowering plasma triglyceride levels. However, the ability to lower triglyceride levels correlates with the reduction of the LDL-C. Notably, the percent

E-mail address: avishayel@clalit.org.il.

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reduction in plasma triglyceride levels is dependent on the baseline triglyceride levels. Given the ability of statins to lower LDL-C and triglyceride/VLDL levels, statin therapy is very effective in lowering apolipoprotein B levels [6–9]. Of note, statins do not lower lipopritein (a) levels and may even increase them [10,11], but modestly increase HDL-C levels, between 5 and 10% [7,12,13].

In addition, statins also have pleiotropic effects that may not be directly related to alterations in lipid metabolism. For example, statins are anti-inflammatory and consistently decrease CRP levels. Others effects include: anti-proliferative, antioxidant, anti-thrombosis, improving endothelial dysfunction and attenuating vascular remodeling. Whether these pleiotropic effects contribute to the beneficial effects of statins is uncertain [14,15].

The various statins have different pharmacokinetic properties, which can explain clinically important differences in their safety and interactions. Most statins are lipophilic except for pravastatin and rosuvastatin, which are hydrophilic. Lipophilic statins can enter cells more easily but the clinical significance of this difference is not clear. Most of the clearance of statins is via the liver and gastrointestinal tract. Renal clearance of statins in general is low with atorvastatin, making this particular drug the statin of choice in patients with significant renal disease. The half-life of statins varies greatly, with pravastatin, simvastatin and fluvastatin having a short half-life (1–3 h) while atorvastatin, rosuvastatin, and pitavastatin having a long one. In patients with statins intolerance, the use of a long-acting statin every other day or 2 times per week has been employed. Short acting statins are most effective when administered in the evening when HMG-CoA reductase activity is maximal, while the efficacy of long-acting statins is equivalent whether given in the AM or PM [16–20].

A key difference between statins is their pathway of metabolism. Simvastatin, and atorvastatin are metabolized by the CYP3A4 enzymes and drugs that affect the CYP3A4 pathway can alter the metabolism of these statins. Fluvastatin is metabolized mainly by CYP2C9 with a small contribution by CYP2C8. Pitavastatin and rosuvastatin are minimally metabolized by the CYP2C9 pathway. Pravastatin is not metabolized at all via the CYP enzyme system [16-19,21].

Many treated patients (vary between 5 and 70%) are statin intolerant (SI); they may not tolerate the full therapeutic statin dose and have adverse effects, mostly muscles symptoms [22]. It should be emphasized that the reported incidence of muscles symptoms was consistently lower in randomized placebo-controlled trials than in observational studies. The recent Self-Assessment Method for Statin side-effects Or Nocebo (SAMSON) trial demonstrated that 90% of adverse symptoms related to statins were also elicited by placebo, a powerful demonstration of the nocebo effect. Importantly, 50% of the study patients were able to successfully reinitiate statin therapy [23]. Never the less, SI is one of the main reasons for stains underuse and the failure to reach the LDL-C recommended target levels [5].

After many years of statin use it was recognized that statins increase the risk of developing diabetes mellitus (DM). In a meta-analysis of 13 trials with over 90,000 subjects, there was a 9% increase in the incidence of DM during follow-up among subjects receiving statin therapy [24]. All statins appear to increase the risk of developing DM, and it seems that they are unmasking and accelerating its development that would have occurred naturally at some point in time. In patients without risk factors for developing DM, treatment with statins does not appear to increase the risk.

While the FDA has mandated warnings regarding statin induced cognitive dysfunction, randomized clinical trials do not indicate a significant association [25–27].

The available data show no increased risk of brain hemorrhage with statin use in primary stroke prevention populations. An increased risk in secondary stroke prevention populations is possible, but the absolute risk is very small and the benefit in reducing overall stroke and other vascular events generally outweighs that risk [28].

Studies have shown that the risk of liver function test abnormalities in patients taking statins is very small. The increases in transaminase levels with statin therapy are dose related with high doses of statins leading to more frequent elevations. At this time, routine monitoring of liver function tests in patients taking statins is no longer recommended. However, obtaining baseline liver function tests prior to starting statin therapy is indicated. If liver function tests are obtained during statin treatment, one should not be overly concerned with modestly elevated transaminase levels (less than 3x the upper limit of normal). If the transaminase is greater than 3x the upper limit of normal the test should be repeated and if it remains $>$ 3x the upper limit of normal, statin therapy should be stopped and the patient be evaluated [29,30].Studies have suggested that the incidence of liver failure in patients taking statins is very similar to the rate observed in the general population (approx. 1 case per 1 million patient years) [31,32]. Thus, statin therapy causing serious liver injury is a very rare event. Never the less, moderate to severe liver disease is a contraindication to statin therapy [29].

Statins are contraindicated in pregnant or lactating women. In women of child bearing age birth control should be discussed and statins should be discontinued prior to conception [29].

3. Ezetimibe

The sources of the intestinal cholesterol are the diet but mainly the bile acid. Ezetimibe prevents cholesterol absorption from the intestine by blocking the Niemann-Pick C1 Like 1 protein, leading to the decreased delivery of cholesterol to the liver, a decrease in hepatic cholesterol content and an up-regulation of hepatic LDL-R [33].

Ezetimibe is used as add-on to statin therapy, as it effectively reduces the LDL-C levels by 15–20% alone, as diet, but up to 50% in combination with statins [34,35]. It is recommended to take one 10 mg tablet a day with food or between meals.

Ezetimibe has few side effects, including: headache and/or diarrhea ($\geq$1%), myalgia and/or raised liver function test results (0.1–1%) and hypersensitivity reactions (rash, angioedema) or myopathy ($<$0.1%) [36].

Ezetimibe lacks significant inhibitor or inducer effects on cytochrome P450 isoenzymes, which explains its limited number of drug interactions. No dose adjustment is needed in patients with chronic kidney disease or mild hepatic dysfunction (Child-Pugh score 5–6). Use in pregnancy and breast feeding is of unclear safety [37].

In the IMPROVE-IT study, involving 18,144 patients with acute coronary syndrome within the preceding 10 days that were randomized to be treated with the combination of simvastatin (40 mg) and ezetimibe (10 mg) or simvastatin (40 mg) and placebo, the Kaplan-Meier event rate for the primary end point [a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization ($\geq$30 days after randomization), or nonfatal stroke] at 7 years was 32.7% in the simvastatin-ezetimibe group as compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference, 2.0 percentage points; hazard ratio, 0.936; 95% CI, 0.89 to 0.99; $P = 0.016$) [38].

Ezetimibe is also available in fixed combinations with simvastatin, atorvastatin, rosuvastatin and bempedoic acid.

4. PCSK9 inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease, mainly expressed in the liver, that targets LDL-R. It leads the receptors to lysosome-mediated degradation, thus diminishing their recycling and decreasing the removal rate of circulating LDL particles with a subsequent increase in LDL-C concentration in the blood. Therefore, reducing the PCSK9 level have a favorable effect on LDL-C levels. [5,39-41].

4.1. Monoclonal antibodies against PCSK9

Two human monoclonal antibodies against PCSK9 (PCSK9 mAbs), alirocumab and evolocumab, were developed, and are under wide use as a therapeutic option in addition to diet, maximally tolerated dose of statins with or without ezetimibe or even alone for patients in high or very high CV risk.

Anti PCSK9 mAbs have been shown to reduce the LDL-C levels markedly and consistently, up to 60%. Also, they have been shown to decreases the levels of apoprotein B by 40 to 50%, lipoprotein (a) by 30 to 40% and triglyceride by 8 to 10%. To increases HDL- C levels by 8 to 10% and apoprotein A1 by 4 to 5% [42,43].

Practically, there are no meaningful differences between the agents, as well as there is no study to compare between them. Alirocumab is supplied in 75 mg or 150 mg single-dose prefilled pen or syringe**.** The recommended starting dose is 75 mg once every two weeks, administered subcutaneously. An alternative starting dose is 300 mg once every four weeks. There is currently no pediatric dosing for this drug. Evolocumab is supplied as a 140 mg/mL and 420 mg/3.5 mL. For adults and children 10 years of age and older with heterozygous familial hypercholesterolemia, the dosing is 140 mg every two weeks or 420 mg once monthly administered subcutaneously. For ones with homozygous familial hypercholesterolemia the dosing is 420 mg subcutaneously once a month but can be increased to 420 mg every 2 weeks if a clinically meaningful response is not achieved in 12 weeks.

Adverse side effects include: Injection-site reactions and nasopharyngitis. There weren't any increased signal for hepatotoxicity, increase in muscle-related complaints or increase in muscle enzymes, nor increased risk of cognitive impairment as well as no clinically significant drug-drug interactions [44,45].

Two multicenter, double-blind, randomized trials defined the favorable CVO of the anti PCSK9 mAbs. The ODYSSEY OUTCOMES study enrolled 18,924 patients with acute coronary syndrome and LDL-C level $\geq$ 70 mg/dL on maximum tolerated statin dose. Alirocumab reduced the primary endpoint (composite of death from coronary artery disease, non-fatal acute myocardial infarction, fatal or non-fatal ischemic stroke or unstable angina requiring hospitalization) as well as deaths from any cause by 15% (ARR 1.6%) over a median follow-up period of 2.8 years [44]. The FOURIER trial enrolled 27,564 patients with stable atherosclerotic cardiovascular disease (ASCVD) and additional risk factors. Treatment with evolocumab reduced the trial's primary endpoint (composite of CV death, acute myocardial infarction, stroke, coronary revascularization or hospital admission for unstable angina) by 15% (ARR 2%) over an average follow-up period of 2.2 years [45]. The results of both studies had shown a low incidence of adverse events without any variations across subgroups.

Sub analysis of the ODYSSEY OUTCOMES study reviled that the higher the patients' risk –the higher the benefit, including: high baseline LDL-C (>100 mg/dl) [44], poly vascular disease and diabetes mellitus [46,47]. Furthermore, alirocumab as a single cholesterol lowering agent was found to be clinically effective [48]. Sub analysis of the FOURIER trial reviled a greater RRR with evolocumab in patients with a recent myocardial infarction (<2 years) compared to patients with a more remote acute myocardial infarction, in patients with $\geq$ 2 prior infarcts compared to patients with 1 prior one and in ones with multivessel CAD compared to patients without it [49].

Recently, extended follow up data have been published. The FOURIER – OLE trial results reviled that long-term LDL-C lowering with evolocumab is associated with persistently low rates of adverse events for over >8 years, with further reductions in CV events compared with delayed treatment initiation [50].

Anti PCSK9 mAbs have been found to affect also the atherosclerotic process. In the Glagov study 968 patients with coronary artery disease were treated with evolocumab or placebo for 76 weeks and underwent serial intravascular ultrasound determinations of coronary atheroma volume. Evolocumab treatment was associated with lower LDL-C levels (36.6 vs 93.0 mg/dL), a reduction in percent atheroma volume (−0.95% vs. the placebo +0.05%) and a greater percentage of patients demonstrating plaque regression (64.3% vs. 47.3%) [51]. The HYUGENS study results showed that statins+ evolocumab produce favorable changes in coronary atherosclerosis consistent with plaque stabilization and regression [52]. The PACMAN-AMI study results indicated that in patients on high-dose rosuvastatin, administration of alirocumab 150 mg biweekly within 24 h after PCI for acute myocardial infarction resulted in a greater reduction in plaque burden and plaque regression at 52 weeks in the non culprit vessel [53]. Similar effects were described in carotid plaques [54,55].

4.2. Small interfering rna agents

The use of small interfering RNA (siRNA) agents represents another strategy to reduce PCSK9 levels. siRNAs block the expression of specific genes with complementary nucleotide sequences by selectively silencing the translation of their complementary target mRNAs [56]. Inclisiran, targeting the 30 UTR of the PCSK9 mRNA, is a long-acting, subcutaneously delivered, synthetic siRNA conjugated to triantennary N-acetylgalactosamine carbohydrates (NAC). It binds to asialoglycoprotein receptors in the liver, resulting in uptake of the Inclisiran and suppression of hepatic PCSK9 production, leading to elevation of LDL-R in the hepatocyte membranes and a subsequent decrease in circulating LDL-C levels [57].

Inclisiran offers infrequent, convenient, twice-yearly dosing which should improve subjects' compliance and adherence to lipid lowering treatment.

The ORION program consists of worldwide trials to evaluate the efficacy and safety of inclisiran in populations with established / high risk for ASCVD or familial hypercholesterolemia [5]. All current studies have provided that over 18 months, Inclisiran is effective with 60% sustained LDL-C levels reduction without any adverse effects related to inflammation, immune activation or clinical immunogenicity nor to liver kidney or muscle side effects. Furthermore,dose adjustments are not required in ones with impaired renal function [58,59].

Recent preliminary results suggest potential benefits for composite MACE reduction [OR (95% CI): 0.74 (0.58–0.94)]. However, the results of ongoing trials are eagerly awaited [60,61].

One of the main limitations in the use of the anti PCSK9 agents is their high costs. In most of the countries, their use is limited to high/very high patients, requires prior authorization according local terms and copayment.

5. Bempedoic acid

After activation, Bempedoic acid (BA) inhibits adenosine triphosphate citrate lyase, resulting in a reduction in acetyl-CoA levels in the cholesterol synthesis pathway upstream of HMG-CoA reductase, leading to an upregulation of LDL-R and a subsequent lowering of LDL-C levels [5]. In addition, activation of AMP-activated protein kinase leads to inhibitory phosphorylation of HMG-CoA reductase and reduces proinflammatory cytokines production chemokines in human macrophages [62,63]. Furthermore, as the skeletal muscle cannot activate the prodrug due to the absence of the enzyme ACSVL1, resulting in the reduction of adverse muscle effects, which often complicate statin therapy [64,65].

Till now, short term studies have shown BA efficacy in lowering LDL-C levels along its safety. In the first phase 2 trial, a 12-weeks study of 177 patients, LDL-C levels were significantly reduced by an average of 18, 25 and 27% at doses of 40, 80 and 120 mg, respectively, along with lowering other atherogenic biomarkers levels, apoprotein B, non-HDL-C and LDL particles [62]. In another study, the efficacy of BA (120 mg and 180 mg) or placebo in addition to ongoing statin therapy was evaluated in 134 patients for 12 weeks. BA lowered LDL-C levels by up to 24% more than placebo (−4.2%); it also reduced hs-CRP, apo B, non-HDL-C and total cholesterol levels more than placebo. No significant reductions

in HDL-C or triglyceride levels were observed. When muscle-related adverse events occurred, the number of drug discontinuations and the number of clinical safety trials were generally similar to placebo [66].

The CLEAR Harmony study included 2230 patients with ASCVD and/or heterozygous familial hypercholesterolemia, LDL-C > 70 mg/dL whilst on treatment with a maximum tolerated dose of statin, randomly assigned to receive BA (180 mg) or placebo. An evaluation after 12 weeks reviled that the mean LDL-C level decreased by 18.1% compared to placebo [67]. The CLEAR Serenity study, a 24-weeks randomized phase 3 trial, evaluated 345 statin intolerant patients, randomly assigned to receive BA or a matching placebo. At week 12, the group receiving BA showed a significant reduction of LDL-C levels from baseline (−21.4%) and a lower incidence of myalgia compared with placebo (4.7% versus 7.2%, respectively), without significant changes in HDL-C and triglycerides levels [68]. The efficacy and safety of BA in combination with ezetimibe was investigated in the CLEAR Tranquilly study, which included 269 participants with SI. Following 4-weeks of ezetimibe 10 mg, patients were randomly assigned to receive in addition BA (180 mg) or placebo for 12 weeks. BA reduced LDL-C levels by 28.5% compared to placebo. The association was found to be safe and effective, with no significant difference in side effects compared to placebo [69].

The most frequent adverse events associated with BA therapy are urinary tract infections (4.5%), reduction in the glomerular filtrate (0.7%), headache (2.8%), hyperuricemia (2.1%) and gout (1.4%) [70]. On the other hand, BA was associated with a reduced risk of new-onset or worsening of diabetes mellitus [71].

The CLEAR out come study enrolled 14,014 participants and is the first ongoing randomized trial to examine the effects of BA on CV events in patients with SI predisposed to or with CVD [72].

Today, BA represents a useful addition to LDL-C lowering therapies in patients on statin therapy or intolerant to them, whose LDL-C levels remain above those suggested by the current guidelines. Its use and the prompt place in the lipid lowering regimens will be clarified after the results of CVO trials will be available.

6. Changes in the lipid lowering regimens paradigm

Today, the argent need to reach very low LDL-C target levels in high / very high CV risk patients along with the availability of new potent agents have led to up dated lipid lowering regimens paradigm, based on the following principals (Table 1):

- ***What matters most is how much, when, and for how long the LDL-C reduction is achieved rather than how it is achieved.***

  Any agent or combination of the current available lipid lowering regimens, that affect the LDL-R, can be used as long as the LDL-C levels are achieved.

- ***From statin monotherapy towards intensive lipid-lowering regimens.***

  Moving from a high-intensity statin approach for all to a high-intensity statin plus ezetimibe approach. It avoids unnecessary steps and allows a more rapid attainment of the target levels with less adverse effects. Single pill combination is better for adherence.
  Re-evaluation of lipids levels 4–6 weeks after initiating treatment regimen.

- ***Early use of PCSK9 Inhibitors combination***

  As in other disciplines, early combination therapy is preferred. It allows to reach LDL-C target levels quickly with less side effects.

- ***"Low LDL-C"*** <30 mg/***dL is safe and effective***

Table 1
The updated lipid lowering regimens paradigm.

- Use any agent or combination, that affect the LDL-R, as long as the LDL-C levels are achieved.
- High-intensity statin plus ezetimibe approach for all - single pill combination is better for adherence.
- *Re*-evaluate lipids levels 4–6 weeks after initiating treatment regimen.
- Early use of PCSK9 Inhibitors combination.
- "Low LDL-C" <30 mg/dL is safe and effective.

Using data from clinical trials, the benefit and risk with low (<30 mg/dL) LDL-c is better known.
In conclusion, the treatment options for reaching the recommended LDL-C target levels have been enlarged and improved during the last decades, with documented favorable effects on the atherosclerotic process and on various CVO. An early combination of lipid lowering agents is advised as "Low LDL-C" levels <30 mg/dL for high/very high CV risk patients is safe and effective.

Declarations of Competing Interest

The author declare he has no conflict of interest.

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