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Lipid-lowering for the prevention of cardiovascular disease in the new era: A practical approach to combination therapy

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ABSTRACT

Low density lipoprotein-cholesterol (LDL-C) is the main etiologic factor for the development and progression of atherosclerotic cardiovascular disease (ASCVD) and LDL-C reduction is a central tenet of ASCVD treatment and prevention. Moreover, ASCVD risk reduction is proportional to the magnitude of LDL-C lowering. Recent European guidelines have recommended a goal of <55 mg/dL (<1.4 mmol/L) for patients at very-high cardiovascular risk, while the U.S. guideline considers an LDL-C ≥70 mg/dL (≥1.8 mmol/L) as a threshold to intensify therapy with the addition of a non-statin therapy to statins. To reach these lower LDL-C goals of <55 mg/dL or <70 mg/dL, combination therapy is necessary in the majority of these patients. Drug combinations, and in particular single-pill combinations, may substantially increase adherence to therapy. Adherence is essential for achieving a clinical benefit and, as many patients discontinue medications, the long-term adherence to lipid-lowering therapy represents a major issue in ASCVD prevention. Secondary prevention or high-risk primary prevention patients, such as those with familial hypercholesterolemia in whom maximally-tolerated statin doses alone would not be anticipated to sufficiently lower LDL-C, would benefit from combination therapy. In current clinical practice, statins with ezetimibe, statins plus PCSK9 inhibitors (with or without ezetimibe), and, most recently statins or ezetimibe with bempedoic acid are the most commonly used combination therapies for LDL-C-lowering. This review outlines the importance of using combination therapy for the achievement of LDL-C treatment goals and discusses some practical approaches for the initiation of combined therapy in patients at the highest risk.

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Introduction

There is overwhelming evidence from genetic, population, and interventional data that low density lipoprotein cholesterol (LDL-C) is causally related to the development of atherosclerotic cardiovascular disease (ASCVD) (1, 2). As such, LDL-C remains a crucial target of both primary and secondary ASCVD prevention strategies, with the recommended intensity of therapy generally matched to the absolute risk of the patient (3). All patients across the risk spectrum benefit from the implementation of favorable lifestyle changes throughout the lifespan, including regular physical activity and healthy diet patterns. However, patients at elevated ASCVD risk are additionally recommended for statin therapy as first line pharmacotherapy for ASCVD prevention (4, 5).

For patients at high or very-high cardiovascular (CV) risk, recent guidelines from the American Heart Association (AHA)/American College of Cardiology (ACC)/Multi-societies and the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) recommend the initiation of a high-intensity statin to achieve an LDL-C reduction of ≥50% (4-6). Additionally, the ESC/EAS guidelines (5) have established risk-based LDL-C goals, with a goal of <55 mg/dL (<1.4 mmol/L) for patients at very-high-risk, while the AHA/ACC guideline (4) considers an LDL-C level of ≥70 mg/dL as a threshold to intensify therapy with the addition of non-statin agents to statins. The general theme across both guidelines is that lower LDL-C is better for longer periods of time. Notably, both sets of guidelines indicate that if patients are unable to reach treatment goals for LDL-C with maximally tolerated statins, add-on therapy with non-statins is recommended (4, 5).

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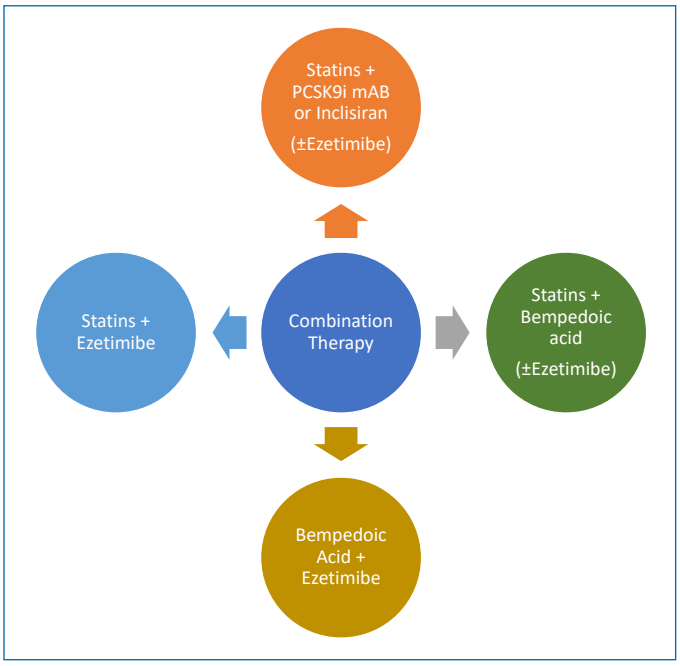

Figure 1 | Options for Combination Therapy.

In this review, we highlight the importance of using combination therapy for the achievement of LDL-C treatment goals and outline some practical approaches. The currently available non-statin therapies for LDL-C lowering that have demonstrated benefits for the reduction in major adverse cardiovascular events (MACE) when added to statins include ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i). Additional effective therapies for LDL-C lowering, but with on-going cardiovascular outcome trials, include bempedoic acid and inclisiran.

Other LDL-C-lowering agents reserved for homozygous familial hypercholesterolemia (HoFH) include evinacumab, mipomersen, and lomitapide, which are beyond the scope of this review, but have been described elsewhere (7). Additionally, icosapent ethyl, a highly purified form of eicosapentaenoic acid (EPA), at a dose of 4 g/day, has also shown incremental benefit for reduction in MACE among patients at high ASCVD risk already treated with statin therapy (8). Icosapent ethyl therapy lowers triglycerides, but not LDL-C, but it is an important therapeutic strategy for patients with high residual risk associated with elevated triglycerides. However, for the purposes of this review, we will be discussing combination therapy for LDL-C lowering.

In current clinical practice, statins with ezetimibe, statins with PCSK9i (with or without ezetimibe), statins with bempedoic acid (with or without ezetimibe), and bempedoic acid with ezetimibe are the most commonly used combination therapies for LDL-C lowering (**Figure 1**).

The current landscape: Suboptimal achievement of LDL-C targets

Unfortunately, many high-risk patients do not achieve guideline-recommended LDL-C levels. The EUROASPIRE IV study (published in 2016) enrolled patients with coronary artery disease (CAD) who had a recent acute coronary syndrome (ACS) or coronary revascularization (9). Despite statin use in 86% of these patients, less than 20% achieved LDL-C of <70 mg/dL (<1.8 mmol/L). There was also a high prevalence of suboptimal control of other risk factors such as persistent smoking, unhealthy diet, inadequate physical activity levels, obesity, and diabetes, and cardiac rehabilitation was substantially underutilized, with an only 50% referral rate (9).

The EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care (the DA VINCI study) enrolled 5,888 patients (3000 primary and 2888 secondary prevention) from 18 countries between 2017-2018 and examined achievement of guideline-recommended LDL-C goals in a real world setting (10). Only about half of patients achieved their LDL-C goal based on the 2016 guideline, and even fewer (33%) would be at target if the newer 2019 ESC/EAS guideline recommendations had been applied. Disappointingly, only 20% and 38% of very-high-risk primary and secondary prevention patients were treated with high-intensity statins. At that time, only 9% of patients were using a combination therapy of moderate-to-high-intensity statins plus ezetimibe and only 1% on PCSK9i combination. However, those using PCSK9i were more likely to have achieved LDL-C goals. These data highlight the implementation gap between guidelines and clinical practice, and emphasize that a greater use of combination therapy is needed so that more high-risk patients are able to achieve LDL-C goals (10, 11).

The Treatment of High- and Very-High-Risk Dyslipidemic Patients for the Prevention of Cardiovascular Events (SANTORINI) registry, which started after the release of 2019 ESC/EAS cholesterol guidelines, recruited 9,606 patients at high- or very-high CV risk requiring lipid lowering therapy (LLT), from 14 European countries, with the objective to determine the effectiveness of current treatment modalities in achieving LDL-C control in a real world setting (12). Despite high-risk status, the mean LDL-C was 95 mg/dL (2.45 mmol/L), 18.6% of patients were not receiving any LLT, and 54% of patients were receiving monotherapy, predominantly statins (13). Only 27% of patients were using combination therapy, including statin plus ezetimibe in 17%, PCSK9i plus an oral medication in 4.1%, and 6% with other oral combinations. As similarly noted in DA VINCI (10), these data continue to show that LDL-C remains above goal in high-risk patients and combination is sorely underutilized (13).

The Getting to an Improved Understanding of Low-Density Lipoprotein-Cholesterol and Dyslipidemia Management (GOULD) registry examined whether LLT was intensified among high-risk patients with ASCVD who were treated with LLT at baseline (14). Among those ASCVD patients with suboptimal control with LDL-C >100 mg/dL, only 22% had their LLT intensified over the next 2 years, with 6.4% having statin therapy intensified, 6.8% having ezetimibe added, and 6.3% with PCSK9i added. The corresponding numbers for those with LDL-C 70-99 mg/dL who underwent LLT intensification was even lower, with only 14% being intensified, including 6.3% placed on higher statin dose, 4.5% with ezetimibe added, and 2.2% with PCSK9i added. Notably, approximately two-thirds of these ASCVD patients remained at suboptimal LDL-C level of >70 mg/dL at 2 years.

There are many, multifactorial, complex reasons why guideline recommended LDL-C levels are not achieved in clinical practice, including: clinician inertia, insufficient patient education, costs, tedious pre-authorization and reimbursement barriers, perceived side effects, fear and mistrust, pill burden, and polypharmacy. Implementation of team-based care approaches (such as pharmacist-led interventions and allied health professionals providing further clinician and patient education), systems protocols (electronic reminders and electronic health record flags) (15), and the use of combination therapy (16) can help overcome some of these barriers.

Adherence: A challenge in clinical practice

Adherence to therapy is essential for achieving a clinical benefit and, as many patients stop taking their medications, the long-term adherence to LLT represents a major issue in ASCVD prevention. This may be particularly true for familial hypercholesterolemia (FH) patients, who need lifelong LLT. Preventive pharmacotherapy does not benefit patients who do not take it and non-adherence translates to poorer outcomes. In a large healthcare utilization registry in Italy, the risk of cardiovascular outcomes was 55% lower among patients who had a high adherence to LLT (proportion of days covered with LLT >75%) compared to those with low adherence (<25% days covered), reinforcing that adherence is a central driver of success (16).

Low statin adherence was also associated with increased risk of mortality among U.S. Veterans Affairs patients (17). In yet another real-world example from a U.K. primary care cohort of patients at high CV risk, patients receiving low-intensity LLT and reduced adherence had the greatest risk for subsequent MACE, whereas the lowest CV risk was observed among adherent patients who were receiving high-intensity therapy (18). This underscores the importance of strategies that can improve both adherence and greater intensity of LDL-C lowering to substantially impact CV risk.

Several studies have shown that combination therapies, and in particular fixed-dose combination therapies, may substantially increase the adherence to treatment (16, 19).

Incremental ASCVD reduction conferred by lower LDL-C

As previously noted, LDL-C levels are the main etiologic factor of atherosclerosis, and LDL-C reduction is the major goal of ASCVD treatment and prevention. Every 39 mg/dL (1 mmol/L) reduction in LDL-C confers an approximate 21% [RR 0.79 (0.77-0.81)] reduction in major vascular events, and more intensive LLT has consistently shown further CV benefits (20). For example, a meta-analysis by the Cholesterol Treatment Trialists Collaboration of 5 randomized clinical trials (RCTs) including over 39,000 participants demonstrated that a more intensive statin regimen, compared to less intensive statin therapy, conferred a 15% (95% CI 11-18%) greater reduction in MACE (21). The main determinant of risk reduction in statin RCTs was the absolute LDL-C reduction, and there was no threshold effect, meaning that further LDL-C lowering conferred further reduction in MACE.

A more recent meta-analysis examining 11 trials and over 130,000 participants compared a more intensive vs a less intensive LLT strategy (22). The more intensive LLT group was defined as treatment regimens to achieve LDL-C <70 mg/dL (using high-intensity statins, ezetimibe plus statins, or PCSK9i) vs a less intensive LLT strategy defined as treatment with less potent active control or placebo that conferred higher achieved LDL-C levels ≥70 mg/dL. This analysis similarly confirmed further benefits in the reduction of all-cause mortality [RR 0.94 (95% CI, 0.89-1.00)], CV mortality [RR 0.90 (0.81-1.00)] and MACE [RR 0.89 (0.84–0.93] with the more intensive LLT regimen (22). Notably, these benefits were achieved without increasing the risk for incident cancer, diabetes mellitus, or hemorrhagic stroke (22). The risk reduction in ischemic endpoints and safety were independent of baseline LDL-C or the specific drug therapy.

Notably, the degree of LDL-C lowering itself matters rather than drug class per se, as all therapies that work by up-regulating the LDL receptor reduce ASCVD risk proportionally to their magnitude of LDL-C (and apoB) lowering (23).

Even with the use of a high-intensity statin, patients may not achieve the anticipated 50% reduction in LDL-C. For example, in the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) primary prevention trial examining 20 mg/day dose of rosuvastatin, only 46% of patients achieved a ≥50% reduction in LDL-C. In addition, 43% achieved a reduction of only >0 but <50%, and 11% of patients experienced no reduction or an increase in LDL-C (24). Many factors may contribute to a suboptimal response, including genetic factors, but also issues related to adherence and persistence to therapy.

Therefore, high-intensity statin monotherapy may not be sufficient in many patients. For these individuals at high- or very-high CV risk, there are multiple benefits for use of combination LLT. For one, combination therapy takes advantage of the synergistic effect of drugs acting on different aspects of LDL metabolism, which is beneficial in patients who cannot achieve adequate LDL-C lowering on high-intensity therapy. Furthermore, although high-intensity statin is the guideline recommended intervention and is tolerated by the majority of patients, there are some patients that report limiting side effects. Combination therapy may help facilitate obtaining similar LDL-C-lowering efficacy using lower statin doses if needed to reduce adverse events that are more prevalent with higher statin doses, such as muscle symptoms, increase of liver enzymes, or diabetes. Higher tolerability may lead to higher adherence, which can be further reinforced by the use of the fixed-dose combinations. Fortunately, multiple LLT combinations are currently available.

Which patients might be good candidates for combination?

Heterozygous FH (HeFH) patients, statin intolerant patients, and patients at high CV risk who are unable to achieve recommended LDL-C goals on maximally tolerated statin doses all represent excellent opportunities to use combination therapy.

HeFH is a genetic disorder, typically with a mutation in one allele of either the *LDLR*, *APOB*, or *PCSK9* genes (7). HeFH patients have life-long elevated LDL-C levels (about two times higher than the general population) and a substantially increased ASCVD risk that occurs at an earlier onset in life than age-matched peers (7, 25). Although statins are the main-stay of treatment in these patients, many HeFH patients are unable to successfully reach optimal LDL-C levels even with maximally tolerated statins, and require add-on therapy.

Despite the above considerations, it should be emphasized that the vast majority of patients are able to tolerate statins, a very safe class of medications. The risk of statin-induced serious muscle injury such as rhabdomyolysis is <0.1%, the risk of serious hepatotoxicity is 1 in 100,000, and the risk of new-onset diabetes mellitus induced by statins is ~0.2% per year depending on underlying diabetes risk of the population (26). Nevertheless, some patients are unable to tolerate sufficient or any statin therapy and need alternative pharmacotherapy for adequate LDL-C lowering. In real-word data, among 5,696 patients with a clinical indication for statin therapy, there were 1511 individuals (26%) not on statin treatment, of which 31% had discontinued their therapy and 55% of those who had stopped statin therapy did so due to perceived effects (27). In an n-of-1 trial (a crossover design where patients served as their own controls) enrolling statin intolerant patients, 90% of the statin-associated muscle symptoms were also elicited by the placebo – a phenomenon called the "nocebo effect" (28). Many patients can tolerate statin therapy when offered a re-challenge and this should be tried first. Nevertheless, the nocebo effect notwithstanding, the perceived side effects from statins are still very real to many patients who may down-titrate or discontinue their statin treatment, leaving them vulnerable to the ASCVD risk related to poorly controlled atherogenic dyslipidemia. In

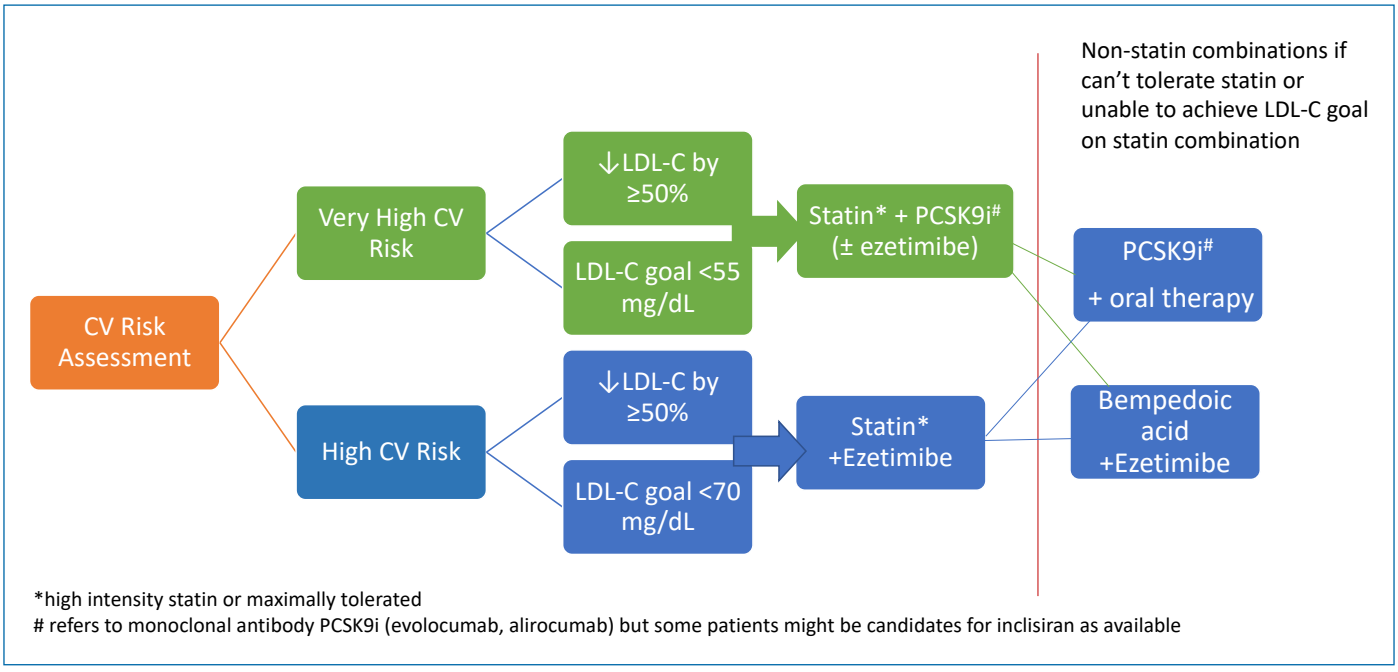

Figure 2 | Candidates for combination therapy.

consideration of the above factors, a combination of various agents may be needed to achieve desired LDL-C levels.

Additionally, even in patients who are optimally treated with statin therapy, there is significant residual risk with recurrent CV events, which can be further reduced by further LDL-C lowering (29-31). Secondary prevention patients or high-risk primary prevention patients in whom maximally tolerated statin doses alone do not sufficiently lower LDL-C, or patients who cannot take statins would benefit from combination therapy. Very-high-risk secondary prevention patients per the AHA/ACC guideline include those with recent ACS, history of myocardial infarction (MI), ischemic stroke, or symptomatic peripheral artery disease (PAD) with at least one other major risk factor, whose therapy should be intensified if the LDL-C remains above 70 mg/dL (4).

The ESC/EAS guidelines set goals of <55 mg/dL and <70 mg/dL for individuals at very-high-risk and high-risk, respectively (**Figure 2**) (5). "Very-high-risk" category includes individuals with documented ASCVD (prior ACS, stable angina, prior revascularization, stroke/TIA, PAD), but also those with ASCVD unequivocally demonstrated by imaging such as multivessel CAD with >50% stenosis seen on invasive coronary angiogram or coronary computed tomography angiography (CCTA) or significant plaque on carotid ultrasound (5). Additional very-high-risk patients include those with diabetes who have evidence of target organ damage or patients with diabetes and multiple major risk factors, early onset type 1 diabetes of long duration (>20 years), severe chronic kidney disease (CKD), a SCORE ≥10% for 10-year risk of fatal CVD, and FH with ASCVD or a major risk factor. "High-risk" category per the European guidelines includes patients with a single markedly elevated risk factor, FH without other risk factors, patients with diabetes without target organ damage but with at least one other risk factor or long duration of diabetes, moderate CKD, or a SCORE 5-10% 10-year risk of fatal CVD (5). In order to reach these more intensive LDL-C goals of <55 mg/dL or <70 mg/dL, combination therapy will likely be necessary in the majority of these patients.

Which types of combination therapy?

The most commonly used combination therapy is statin plus ezetimibe. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), studying high-risk patients after a recent ACS event, demonstrated that patients randomized to ezetimibe added to a statin achieved lower LDL-C (mean 54 mg/dL) compared to statin monotherapy (mean LDL-C 70 mg/dL) and experienced a 2% lower absolute risk and 6% lower relative risk of subsequent MACE. Moreover, the number needed to treat was only 50 to prevent one event (29). Indeed the subsequent 2018 AHA/ACC guideline for lipid management then endorsed the addition of ezetimibe to statin for patients at high- or very-high-risk if the LDL-C remained above a threshold of 70 mg/dL, and if PCSK9i was to be considered, it was recommended to start ezetimibe first (4). This latter recommendation of starting ezetimibe before PCSK9i likely was driven by cost concerns. It should be noted that there is now a combination pill of rosuvastatin 10-40 mg + ezetimibe 10 mg that is commercially available, which can reduce pill burden. The combination of rosuvastatin with ezetimibe can confer up to 60-75% reductions in LDL-C with a good safety profile (32).

In a large registry from Italy, patients who were prescribed a single pill combination (statin+ezetimibe) were 87% more likely to have high adherence to LLT compared to patients who were prescribed both pills separately (16). This advantage of a single-pill combination was seen across all age, sex, and clinical risk groups.

Statin plus PCSK9i

PCSK9i therapy using monoclonal antibodies reduces LDL-C by 50% to 60% when administered as monotherapy or when added to a baseline statin therapy (30, 31, 33). The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) (30) and the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment

With Alirocumab (ODYSSEY OUTCOMES) (31) trials of PCSK9i evaluated evolocumab and alirocumab, respectively, among patients with ASCVD with baseline LDL-C ≥70 mg/dL. In these two trials, the background use of statins was high, and yet the benefit of PCSK9i was incremental to that of statins with a significant 15% reduction in MACE in both trials. In FOURIER, at baseline, nearly all patients were on background statin (69% high-intensity, 30% moderate-intensity), 5% also on ezetimibe, with mean baseline LDL-C of 92 mg/dL (30). In ODYSSEY OUTCOMES, at time of randomization 89% of patients were taking high-intensity statins and had a mean LDL-C of 92 mg/dL (31).

PCSK9i requires administration by injection once or twice a month. Access to PCSK9i had historically been challenging because of the requirement of prior authorization, high costs of the medication, and patients having LDL-C levels below the payer-specific threshold for monoclonal antibodies. However, with cost reduction, access and authorization approvals have become easier over time.

Inclisiran is a small interfering RNA that inhibits PCSK9 through a different mechanism than the aforementioned monoclonal antibodies. Based on ORION-10 and -11 trials, inclisiran was shown to confer a 45-55% reduction in LDL-C (34). Inclisiran is delivered by subcutaneous injection just twice a year, which may translate into improved adherence conferring more sustainable lower LDL-C levels, thus being particularly beneficial for young adults such as those with FH. However, the CV outcome trial (ORION-4, NCT03705234) is still ongoing. Inclisiran was recently approved by the U.S. Food and Drug Administration (FDA) in December 2021 as a treatment to be used along with diet and maximally tolerated statin therapy for adults with heterozygous FH or clinical ASCVD who require additional LDL-C lowering.

Statin plus bempedoic acid

Bempedoic acid is an oral inhibitor of the cholesterol synthesis pathway targeting adenosine triphosphate citrate lyase (ACL), an enzyme upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), the target of statin therapy (35). Bempedoic acid has been approved by the FDA for patients with ASCVD or HeFH who require additional LDL-C lowering. Bempedoic acid is a pro-drug, and the enzyme required for its activation is only expressed in the liver and not in skeletal muscle tissue, so bempedoic acid has not been associated with muscle-related adverse side effects that have been described with statins (36). This makes it a potentially attractive oral option for patients with statin intolerance, but has been demonstrated to further reduce LDL-C even on top of statin therapy. Bempedoic acid should not be used with simvastatin doses greater than 20 mg or pravastatin doses greater than 40 mg.

The CLEAR Wisdom trial enrolled adults at high ASCVD risk with LDL-C level ≥70 mg/dL on maximally tolerated lipid-lowering therapy and showed that bempedoic acid conferred an additional 15% reduction in LDL-C (37). Furthermore, the CLEAR Serenity trial examined bempedoic acid in patients with statin-intolerance and showed a greater reduction in LDL-C of 21% compared to placebo (38). Reductions in LDL-C are even greater in combination with ezetimibe. In a trial evaluated a fixed-dose combination (bempedoic acid 180 mg/ezetimibe 10 mg once daily) or placebo added to stable background statin therapy, the fixed-dose combination reduced LDL-C by 36% (39). These data suggest that bempedoic acid and ezetimibe are more effective when used together, and this fixed-dose combination may be an attractive option to reduce overall pill burden for patients (40). Additionally, across all these trials, bempedoic acid has been consistently shown to reduce high sensitivity C-reactive protein (hsCRP) as well (35, 39). The CV outcome trial for bempedoic acid is on-going (CLEAR OUTCOMES, NCT02993406); this trial enrolled patients who are at high risk for ASCVD but who are statin-intolerant, with approximately 50% of participants being women.

Other oral combinations

Bile acid sequestrants are oral agents that can lower LDL-C by about 15-20% (41). However, bile acid sequestrants can raise triglyceride levels, cause gastrointestinal side effects such as constipation, and block absorption of other medications, thereby limiting their contemporary widespread use. Similarly, niacin has also fallen out of favor due to adverse side effects, and the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial did not demonstrate any benefits of the addition of niacin to a background of statin therapy for further MACE lowering (42).

Conclusions

LDL-C plays a central role in ASCVD development and its progression. It is the magnitude of LDL-C lowering (and not the drug class per se) that is associated with reduced risk of ASCVD outcomes. Since the anticipated degree of LDL-C lowering is established for each specific drug class, and based on an individual's baseline LDL-C and clinical risk profile, it can be predicted from the onset which high-risk patients would likely require combination therapy to achieve the newly recommended more intensive LDL-C levels of <55 mg/dL and <70 mg/dL. Commonly, statin monotherapy is initiated first. However, given substantial clinical inertia, LLT titration and intensification have been demonstrated to be poor in real world practice and LDL-C targets are not met in a substantial number of high-risk patients. One can get to LDL-C goals quicker and more efficiently with early implementation of combined therapies. Fixed dose combination single-pill therapies where available (i.e., the rosuvastatin+ezetimibe and the bempedoic acid+ezetimibe preparations) maybe attractive options for patients who desire to reduce overall pill count. With PCSK9i administered just once or twice a month and inclisiran administered just twice a year, this further can help achieve intensive LDL-C lowering with reduced burden of a daily medication. For patients at high- or very-high CV risk, combination LLT is better together and anticipated to further reduce ASCVD morbidity and mortality in high-risk populations.

Disclosures/Conflicts of Interest

EM reports Advisory Boards for NovoNordisk, Novartis, Astra Zeneca, Amarin, Bayer, Boehringer Ingelheim and Esperion.

KCF reports being consultant for Amgen, Novartis, Medtronic

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Ethical review

As this article was a literature review of published papers and did not involve enrollment of study participants, no ethical review board approval was required.

Authorship Roles

The concept and design for paper was by EDM and KCF. EDM drafted the first draft and KCF provided critical input to the manuscript draft for intellectual content and approved final document.

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