


REVIEW

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2024 Egyptian consensus statement on the role of non-statin therapies for LDL cholesterol lowering in different patient risk categories

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Abstract

Background The new millennium has witnessed increased understanding of cardiovascular (CV) risk factors and improvement in atherosclerotic cardiovascular disease (ASCVD) management. The role of LDL cholesterol and other atherogenic lipid particles in the development of atherosclerosis is now beyond doubt.

Main body Statins have been widely used and recommended in guidelines for preventing and managing ischemic events. However, statins have side effects, and many patients do not achieve their low-density lipoprotein cholesterol (LDL-C) goals. In recent years, non-statin lipid-lowering agents have gained increasing use as adjuncts to statins or as alternatives in patients who cannot tolerate statins. This consensus proposes a simple approach for initiating non-statin lipid-lowering therapy and provides evidence-based recommendations. Our key advancements include the identification of patients at extreme risk for CV events, the consideration of initial combination therapy of statin and ezetimibe in very high-risk and extreme-risk groups and the extended use of bempedoic acid in patients not reaching LDL-C targets especially in resource-limited settings.

Conclusions Overall, this consensus statement provides valuable insights into the expanding field of non-statin therapies and offers practical recommendations to enhance CV care, specifically focusing on improving LDL-C control in Egypt. While these recommendations hold promise, further research and real-world data are needed for validation and refinement.

Keywords Non-statin therapies, LDL cholesterol lowering, Patient risk categories

Background

Cardiovascular diseases (CVD) have been a leading cause of death and disability worldwide for many years **1**. In 2021, the Global Burden of Disease (GBD) study linked elevated low-density lipoprotein cholesterol (LDL-C) levels to 3.81 million deaths from CVD and other causes. **2**

Statins have long been the first option for LDL-C reduction and have led to a revolutionary improvement in CV outcomes, particularly for high-risk patients. Meta-analyses of randomized clinical trials showed

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that 1 mmol/L reduction in LDL-C cardiovascular (CV) risk by 21%. 3

However, studies have shown that many patients fail to achieve the recommended LDL-C goal, despite being on high-intensity statins [4–8]. This suboptimal response to statins can be due to various factors, including genetic factors, statin intolerance and physician inertia [9–12]. Patients with familial hypercholesterolemia (FH) often require additional therapies beyond high-intensity statins to effectively lower LDL-C levels. 13

Challenges such as incomplete adherence, statin intolerance and long-term risks faced by those with inadequate LDL-C control have led to a growing emphasis on the development of alternative forms of lipid-lowering therapy (LLT) as an adjunct or alternative to statins. Furthermore, there is growing interest in early combination lipid-lowering management approaches 14, as they offer several benefits, such as incremental LDL-C lowering, reduced risk for side effects and improved tolerability and adherence 15, 16. In the DYSIS-EGYPT study, almost one-third of patients (30%) were receiving other lipid-lowering therapies, primarily ezetimibe (23.7%), but also fibrates (8.3%), bile acid sequestrants (1.0%) and nicotinic acid (0.3%). However, the percent of patients reaching LDL-C goals was overall low 17. The evolving landscape of non-statin therapies will continue to provide patients with more therapeutic options for reducing CV risk, each with unique indications, advantages, disadvantages and evidence base. 18, 19

Despite evidence of the effectiveness of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9-I), a large multicenter project revealed that they were prescribed to less than 1% of over 3.5 million patients 20. This low prescription rate can be attributed to factors such as cost, initial lack of outcome data, prior authorization requirements and lack of insurance approval 21. Ultimately, the high cost of treatment limits the use of PCSK9-I. 22

Egypt is classified as a country with a very high CV risk, with CVD accounting for 46.2% of non-communicable disease-related deaths in 2017 23. The Egyptian CardioRisk project published in 2020 found that 51% of Egyptians had premature acute coronary syndrome (ACS) 24, 25, and dyslipidemia was a prevalent modifiable risk factor, affecting 48.2% of individuals 26. Given the limited resources in Egypt, alternative approaches are necessary to reduce CV risk and identify specific high-risk populations that can benefit from costly medications.

Main text

Rationale for use of non-statins

The response to statins and the achievement of LDL-C goals in primary and secondary prevention patients have been the subject of several recent studies [4–8]. The TERESA study revealed that only 31.1% of patients achieved the risk-based LDL-C goals, despite being on high-intensity statins, with nearly 70% of very high-risk patients failing to reach the recommended LDL-C goals 8. Statin hyporesponsiveness can be attributed to various factors, including rare genetic variants in lipoprotein-related or drug metabolism genes 9, 10. Before considering primary statin resistance, other potential causes such as analytical issues with LDL-C measurement and the presence of common lipid disorders [FH, elevated lipoprotein (a) (Lp(a)) and secondary dyslipidemias] should be ruled out. 13

Nonetheless, the most common reason for suboptimal response to statin therapy is the lack of compliance due to statin intolerance. The lipid management registry showed that over 50% of former statin users discontinued the medication due to perceived side effects, primarily muscle-related symptoms 11. Similarly, a recent meta-analysis estimated that between 5 and 17% of patients discontinue statins due to medication side effects, which is significantly higher than rates observed in clinical trials. 12

The SANTORINI study assessed lipid management in 9044 patients after the 2019 ESC/EAS guidelines update. It found that 80% of high- and very high-risk patients did not meet LDL-C goals. 27

In the DA VINCI study which involved 5888 patients, 54% of patients achieved the 2016 risk-based goal, while 33% achieved the 2019 goal. High-intensity statin monotherapy was used in 20% of very high-risk primary prevention patients and 38% of secondary prevention patients. Combination therapies, including ezetimibe (9%) or PCSK9-I (1%), were used less frequently. The corresponding 2016 and 2019 goal attainment was 53% and 20% for moderate–high-intensity statin combination with ezetimibe, and 67% and 58% for PCSK9-I combination. 28

Therefore, there are persistent gaps between clinical guidelines and clinical practice for lipid management across the world. To address these gaps, greater utilization of non-statin LLT even with optimized statins, especially for patients at the highest risk, is needed.

In recent years, clinical trials have demonstrated the efficacy of several non-statin agents in lowering LDL-C levels and reducing CV events in specific patient populations [29–47]. Landmark trials have established ezetimibe, PCSK9 monoclonal antibodies and bempedoic acid as non-statin agents that lower LDL-C levels and

provide CV benefits. Additionally, a large-scale outcome trial is underway to evaluate the efficacy of inclisiran. [48](#)

There is growing interest in early combination lipid-lowering management approaches [14](#), as they offer several benefits such as incremental LDL-C lowering, reduced risk for side effects and improved tolerability and adherence [15, 16](#). Combination therapies, especially including a PCSK9-I, have been shown to achieve the recommended LDL-C goals in a higher percentage of very high-risk patients compared to high-intensity monotherapy or statin/ezetimibe combination. [28](#)

Cardiovascular risk stratification

Total CV risk is defined as the likelihood of a person to develop an atherosclerotic CV event within a given time period. It is determined by adding the risk contribution of various CV risk factors present in an individual. Some risk factors, such as a history of a previous atherosclerotic event, represent a very high total CV risk on their own, even in the absence of other risk factors.

There is no universal consensus on the definition of very high-risk patients, but it is recommended to intensify preventive approaches for these patients in all guidelines. The very high-risk patient category definition is different between guidelines. All guidelines base the intensity of their recommendations on the degree of risk. Guidelines differ in their risk calculation systems.

In the American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety (MS) guidelines, risk scores are calculated with pooled cohort equations (PCEs). PCEs calculate the 10-year risk of developing ASCVD by including non-fatal myocardial infarction (MI) or coronary artery disease (CAD) death and fatal or non-fatal stroke, among people free from ASCVD [1](#). In the ACC Expert Consensus Decision Pathway published in 2022 on the use of non-statins, patients with ASCVD were categorized into one of two groups: not at very high risk or at very high risk. Very high-risk patients have a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions. Major ASCVD events include ACS within 12 months, history of MI, ischemic stroke or symptomatic peripheral arterial disease (PAD). High-risk conditions include age ≥ 65 years, heterozygous FH (HeFH), history of prior coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI) outside of the major ASCVD event(s), diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD) (eGFR 15–59 mL/min/1.73 m²), current smoking, persistently elevated LDL-C ≥ 100 mg/dL despite maximally tolerated statin therapy and ezetimibe or history of congestive heart failure (CHF). [2](#)

The European Society of Cardiology (ESC) guidelines described low-, intermediate-, high- and very high-risk categories of ASCVD risk. People were sorted into one of these categories depending on the presence or absence of major risk factors and, in apparently healthy persons, depending mainly on their 10-year CV risk estimation. [49, 50](#)

The ESC guidelines define patients with ASCVD, DM, CKD and individuals with specific risk factors as high- and very high-risk groups automatically. Individuals who do not have these characteristics are considered as apparently healthy people, and management is determined according to risk estimation by the SCORE2 and the SCORE2-Older Persons (SCORE2-OP) model for adults over the age of 69, which calculate the 10-year risk of total CV events. In diabetic patients, CV risk stratification is based on ASCVD, severe target organ damage (TOD) or SCORE2-Diabetes. Management is determined according to age, risk score and region. [49, 50](#)

Ray et al. defined the extremely high-risk patient category as having one of the following characteristics: post-ACS and a history of other vascular event in the past 2 years, PAD, polyvascular disease, multivessel CAD and/or FH. [14](#)

The American guidelines give recommendations for the possible use of the coronary artery calcium (CAC) score if the decision about statin treatment is uncertain in intermediate- and borderline-risk adults. If the CAC score is above 100, it is reasonable to initiate statin treatment. If the CAC score is 1–99, it is reasonable to use statins in individuals > 55 years. If the CAC score is zero, there is no need to use statins as long as higher-risk conditions are absent, but reassessment is suggested in 5–10 years [29](#). Similarly, the ESC guideline states that CAC scoring may be considered to improve risk classification around treatment decision thresholds, and they also consider plaque detection by carotid ultrasound an alternative when CAC scoring is unavailable or not feasible. [51](#)

We endorse the CV risk stratification recommended by the latest ESC guidelines [49, 50](#). However, we recommend distinguishing patients who are at extremely high CV risk from the very high-risk category. We propose defining the extreme-risk patient category by the presence of at least one of the following criteria: (1) multiple major CV events, especially if recurrent within 2 years, (2) one major CV event and multiple high-risk conditions such as current smoking, DM, HTN and CKD, (3) polyvascular disease, (4) multivessel CAD and (5) recent ACS within the past 12 months (Fig. [1](#)).

For patients in the low- to moderate- and high-risk conditions, it is advisable to check for risk modifiers. The presence of these risk modifiers upgrades the

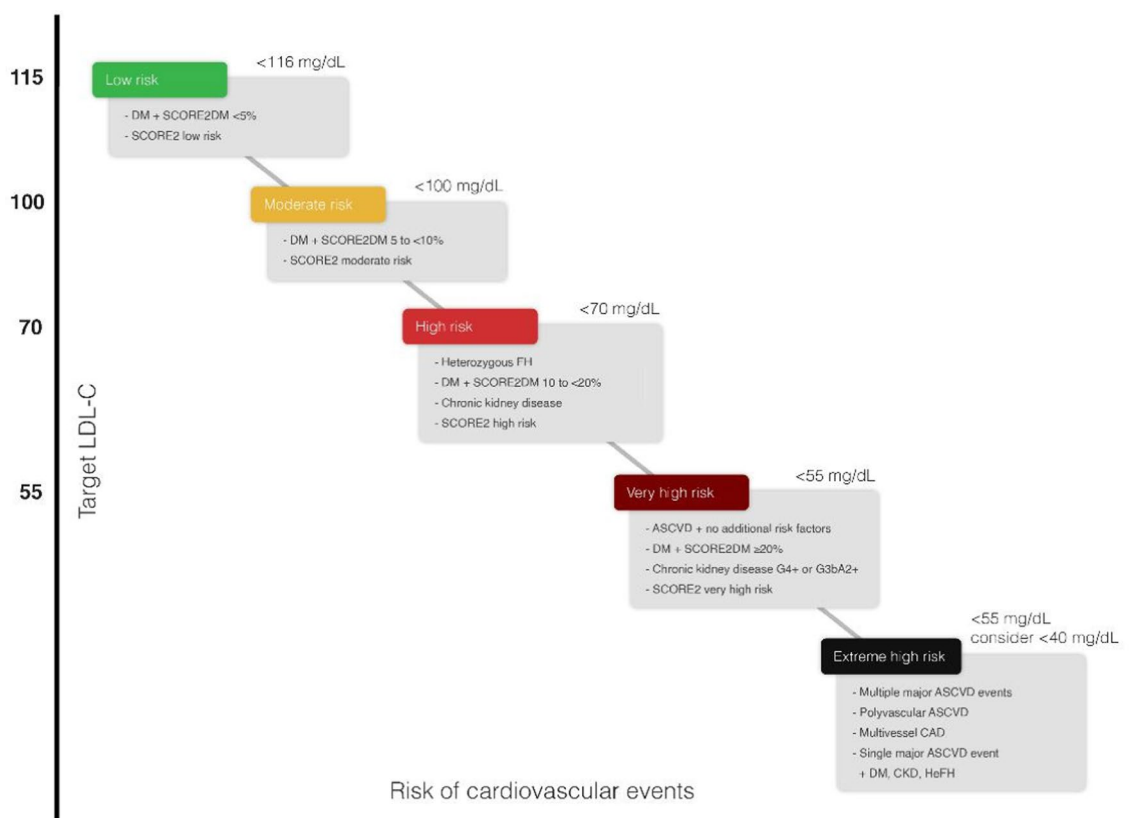


Fig. 1 Patient risk categories and recommended LDL-C goals

patient’s risk category and supports the use of LLT. Risk modifiers include family history of premature ASCVD (men aged <55 years; and women aged <65 years), familial dyslipidemia, metabolic syndrome, CKD, chronic immune-mediated inflammatory conditions, sex-specific conditions (history of premature menopause before age 40 years, pregnancy-related HTN and erectile dysfunction), psychosocial factors, left ventricular hypertrophy, atrial fibrillation, obstructive sleep apnea syndrome, non-alcoholic fatty liver disease, migraine with aura and if measured, CAC score >0 Agatston units (AUs), elevated high-sensitivity C-reactive protein (>2.0 mg/L), high Lp (a) >50 mg/dL and ankle brachial index (ABI) <0.9.

Lipid-lowering strategies

Statins, or hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are widely prescribed and effective in lowering cholesterol levels by inhibiting the enzyme responsible for cholesterol production. However, some patients experience side effects, such as muscle pain or liver abnormalities, leading to discontinuation or reduced adherence. [52](#)

Non-statin options (Fig. 2)

1. Ezetimibe

Ezetimibe inhibits cholesterol absorption at the brush border of the small intestine by binding to the sterol transporter Niemann–Pick C1-Like-1 (NPC1L1). The reduction in cholesterol absorption, when combined with statins, offers a synergistic effect on LDL-C levels lowering. [53](#)

Ezetimibe, given as a monotherapy in a single daily oral dose of 10 mg, reduces LDL-C levels by 15–22% compared to placebo. Adding ezetimibe to statin therapy reduces LDL-C by an additional 21–27%. Ezetimibe decreased triglyceride (TG) by about 8% and increased high-density lipoprotein cholesterol (HDL-C) by about 5%. [53](#)

The IMPROVE-IT trial evaluated the effect of ezetimibe and simvastatin compared with simvastatin alone in patients with ACS. This study which included over 18,000 patients with ACS found that adding ezetimibe to statin therapy lowered

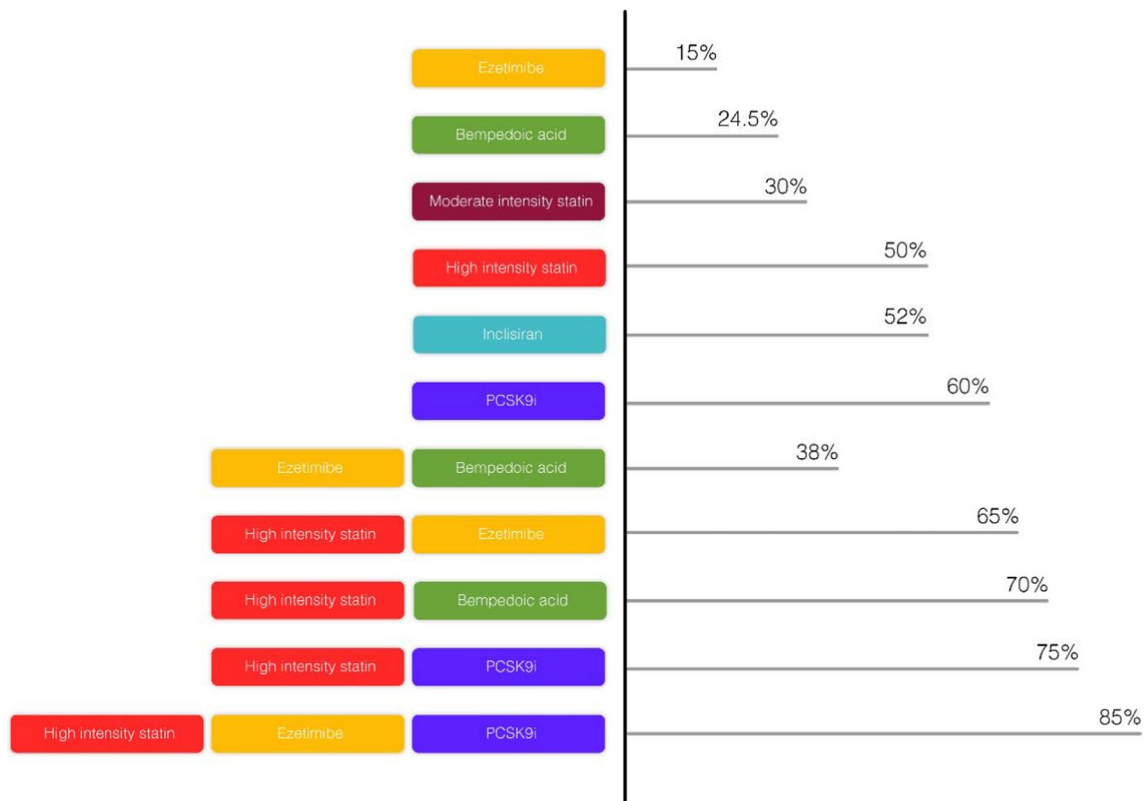


Fig. 2 Efficacy of different lipid-lowering medications as monotherapy or in combination

LDL-C by 24% and the major adverse CV events (MACE) by 2% (absolute risk difference). [54](#)

The US Food and Drug Administration (FDA) gave a category C mark to ezetimibe based on preclinical data from animal studies; however, no enough data is available to support the use of ezetimibe in pregnancy and lactation. The use of ezetimibe in children is not studied. [55](#)

The most frequent side effects of ezetimibe are diarrhea (4%) and headache (2%) while liver injury is extremely rare. Ezetimibe use is contraindicated in moderate and severe liver impairment. There is no need for dose modification in renal impairment or mild hepatic impairment. [54](#)

2. PCSK9-targeted therapies

PCSK9 is a protease that degrades LDL receptors in the liver. Human monoclonal antibodies, alirocumab and evolocumab, administered through subcutaneous injections bind to PCSK9, preventing it from binding to LDL receptors. Inclisiran is a synthetic small interfering RNA (siRNA) that targets hepatic production of PCSK9. By preventing the destruction of the LDL receptors, these drugs

enhance the ability of the liver to clear LDL-C from the bloodstream significantly reducing its level. [56](#)

Multiple trials have demonstrated not only the potency of PCSK9-I in significantly lowering LDL-C levels [56](#), but also their efficacy in improving CV outcomes with reduction in MACE, including heart attacks and strokes.

In 2017, the FOURIER trial demonstrated that inhibition of PCSK9 with evolocumab on a background of statin therapy was efficacious in patients with stable ASCVD and additional high-risk features. The ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial demonstrating the benefits of PCSK9 inhibition with alirocumab on a background of statin therapy in patients with ACS. [31, 57](#)

In a pooled patient-level analysis of 3660 patients in phase 3 trials of inclisiran (ORION-9, ORION-10 and ORION-11), the drug demonstrated a mean placebo-corrected change in LDL-C at day 510 of 50.7% (95% CI 52.9% to 48.4%; $P < 0.0001$). The corresponding time-adjusted mean change in LDL-C was 50.5% (95% CI 52.1% to 48.9%; $P < 0.0001$) [58](#). Inclisiran was FDA approved in December 2021 and is indicated

as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or ASCVD who require additional lowering of LDL-C [59](#). The recommended dosage of inclisiran, in combination with maximally tolerated statin therapy, is 284 mg administered as a single subcutaneous injection initially, again at 3 months, and then every 6 months thereafter. The effect of inclisiran on CV morbidity and mortality has not been determined. However, we are waiting the results of two important CV outcomes trials, ORION-4 (A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease) and VICTORION-2P (A Randomized, Double-blind, Placebo-controlled, Multicenter Trial, Assessing the Impact of Inclisiran on Major Adverse Cardiovascular Events in Participants With Established Cardiovascular Disease), which are currently in progress. [59](#)

Generally, PCSK9-I has demonstrated a favorable safety profile. However, like any medication, they may be associated with certain side effects, including injection-site reactions.

The cost of the PCSK9-I remains a major obstacle in the large-scale use of these drugs. Another challenge is the need for subcutaneous injections. Efforts to address these challenges and ongoing research into alternative administration methods may further broaden the accessibility and utilization of these inhibitors. [60](#)

3. Bempedoic acid

Bempedoic acid is a prodrug that is activated in the liver. It competitively inhibits ATP citrate lyase (ACL), an enzyme that operates upstream of HMG-CoA reductase. This allows bempedoic acid to effectively lower LDL-C levels.

Bempedoic acid and the fixed-dose combination with ezetimibe were FDA approved in 2020 and are indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or ASCVD who require additional lowering of LDL-C. [61](#)

The daily dose is 180 mg, administered orally, once daily. No renal or hepatic dose adjustment is required for mild or moderate renal or hepatic impairment. Bempedoic acid is not studied in severe renal impairment ($eGFR < 30$ ml/min/m²) and severe hepatic impairment (Child–Pugh C). No data is available on the use of bempedoic acid in pregnancy or lactation in humans. However, no teratogenicity was detected in animal studies.

In the clear outcome trial, involving almost 14,000 patients for primary or secondary prevention,

bempedoic acid significantly reduced LDL-C levels by 18%. This reduction in LDL-C levels translated into a 21% lower risk of MACE, including heart attack, stroke and CV death. Bempedoic acid also lowers hs-CRP; however, it does not significantly affect TG and Lp(a) levels. [62](#)

Bempedoic acid has a favorable safety profile. The most common side effects include hyperuricemia, nasopharyngitis and upper respiratory tract infection. The rare occasion of tendon rupture, in clear outcome trial, was non-significant; however, bempedoic acid should be discontinued immediately if the patient experiences tendon rupture. Consideration of an alternative therapy is advised in patients with a history of tendon disorders or tendon rupture. Muscle-related side effects are usually related to the concomitant use of high-intensity statin, and this goes in favor of the use of bempedoic acid in statin intolerance. [62](#)

Bempedoic acid offers a valuable addition to the available cholesterol-lowering therapies. It provides an effective, relatively cheap and well-tolerated option for patients with high LDL-C levels who cannot tolerate statins or require additional LDL-C lowering beyond what statins can provide. [62](#)

4. Fibrates

Fibrates, such as fenofibrate, primarily target TG levels and raise HDL-C. They are often considered in patients with hypertriglyceridemia or mixed dyslipidemia. Fibrates may also be used in combination with statins for comprehensive lipid management. The positive effects fenofibrate on diabetic retinopathy may have important clinical implications. The Accord-Eye study, using fenofibrate combined with statin, demonstrated a reduced progression of diabetic retinopathy. [63](#)

5. Bile acid sequestrants

Bile acid sequestrants bind to bile acids in the intestine, preventing their reabsorption. This process enhances the clearance of LDL-C from the blood. While effective, these agents may be associated with gastrointestinal side effects, impacting their tolerability. [64](#)

6. Evinacumab

Angiopoietin-like protein 3 (ANGPTL3) pharmacologic inhibition reduces LDL-C levels independently of the LDL receptor. Evinacumab, a human monoclonal antibody that inhibits of ANGPTL3, was initially evaluated in patients with homozygous FH (HoFH), who may have absent or defective LDL receptors [65](#). In 2021, evinacumab received FDA approval and is indicated as an adjunct to other LDL-C-lowering therapies for the treatment

of adult and pediatric patients, aged 12 years and older, with HoFH 66. Evinacumab is also being investigated for the treatment of patients with severe hypertriglyceridemia.

7. Lomitapide and mipomersen

Lomitapide is a selective inhibitor of the microsomal triglyceride transfer protein (MTP) and reduces LDL-C levels by approximately 40%. It may cause elevations in liver transaminases and hepatic steatosis with the risk for progressive liver disease. 67

Mipomersen is an antisense oligonucleotide that inhibits the production of apoB-100 and lowers LDL-C by approximately 37%. Both medications represent new therapeutic approaches for patients with HoFH who do not reach LDL targets with statins. 67

LDL apheresis

It selectively removes apo B-containing lipoproteins, producing an acute reduction in LDL-C. The FDA-approved indications include: patients with FH unresponsive to pharmacologic and dietary management who are either functional homozygotes with an LDL-C > 500 mg/dL, functional heterozygotes with no known CV disease but an LDL-C > 300 mg/dL or functional heterozygotes with known CVD and LDL-C > 200 mg/dL 68. The extracorporeal technique is performed weekly or biweekly with an average LDL-C reduction of ~50–60% of the original values. Adverse effects include problems with venous access; transient hypotension and bleeding. CV outcomes trials are limited due to lack of randomized controlled trials of these very high-risk patients. 69

Approach to LDL-C lowering according to patient risk category

According to the 2019 ESC guidelines, all patients in the very high-risk category should be managed similarly with a target LDL-C goal of below 55 mg/dL. Only patients with recurrent major ASCVD events within 2 years, despite optimal risk reduction measures, should be considered for a lower LDL-C target of below 40 mg/dL, as a class IIb recommendation 5. On the other hand, the 2022 ACC Expert Consensus Decision Pathway sets the LDL-C goal for high-risk patients with clinical ASCVD at below 70 mg/dL and for those at very high risk at below 55 mg/dL.

However, evidence from the FOURIER 6 and ODYSSEY 7 trials suggest that patients at extreme CV risk may benefit from even lower lipid targets and more aggressive CV risk reduction measures compared to the rest of the very high-risk category. These patients may also benefit from the use of combination therapy as an

initial treatment approach. Ray et al. encouraged this approach advocating the idea of the use of triple initial therapy in the form of statins, ezetimibe and PCSK9-targeted therapy in the extremely high-risk cohort. 14

The WHO classified the Egyptian population as having a very high risk of CVD mortality 23. The DYSIS study revealed that the achievement of LDL-C goals in the Egyptian cohort was lower compared to other populations, with only 33% of patients meeting the target. The above-target LDL-C levels were found in only 28% of high- and very high-risk patients and 50% of moderate-risk patients 17. This highlights the need for amended strategies to address poor LDL-C management in Egypt and encourage a lower LDL-C therapeutic goal.

Based on the data presented, we have formulated the following recommendations for ASCVD risk management. Firstly, it is crucial to distinguish individuals at extremely high ASCVD risk from the rest of the very high-risk category. For these individuals, we suggest initiating combination therapy with a high-intensity statin, if tolerated, and ezetimibe as an initial approach. The LDL-C target for this group should be below 55 mg/dL, with consideration of a lower initial target of below 40 mg/dL on an individual basis. Initial combination therapy with ezetimibe may also be considered in the very high-risk category when a 50% reduction in LDL-C is not expected to get the patient to target. For other risk categories, we advise following the recommendations outlined in the ESC dyslipidemia guidelines.

If additional LDL-C lowering of less than 20–30% is required, particularly in the non-acute setting, the addition of bempedoic acid may be considered. However, if a greater reduction in LDL-C is necessary for individuals in very high- or extreme-risk categories, PCSK9-targeted therapy should be considered. Although there have been no large-scale studies comparing PCSK9-I and bempedoic acid to date, both medications have been studied in thousands of patients with various risk profiles and have each demonstrated the ability to achieve their primary hard endpoints, resulting in a significant reduction in CV morbidity and mortality. It is also noteworthy that, while not yet included in the guidelines, bempedoic acid can serve as an option for optimizing lipid control in resource-limited settings.

In patients who are elderly, at risk of myopathy, having CKD or having partial statin intolerance, we advise to consider initiation of LLT with a combination of moderate-intensity statin and ezetimibe. In case the statin intolerance is complete, an initial combination of ezetimibe and bempedoic acid can be considered. Further addition of PCSK9-targeted therapy may be needed according to the LDL-C level achieved. Finally,

the clinician's selection of the appropriate therapy requires discussion and a shared decision-making with the patient to ensure personalized and effective management of ASCVD risk (Fig. 3).

Monitoring of response to lipid-lowering therapy

Both the European and American guidelines recommend assessing the response to pharmacological therapy at 4–12 weeks from initiation or adjustment of therapy. This initial follow-up allows for the evaluation of treatment effectiveness and any necessary



Fig. 3 Risk categories, LDL-C goals and suggested management strategies

adjustments. Subsequent follow-up intervals after the LDL-C goal is attained differ between guidelines. The European guidelines suggest 6–12 months for monitoring, while the American guidelines recommend 3–12 months. 29, 51

The ESC guidelines recommend shorter initial follow-up intervals of 4–6 weeks after ACS to ensure early and proper LDL-C goal achievement 51. This recommendation is based on the need for closer monitoring during the early stages of recovery from the acute event. Our writing committee also advocates comparable initial follow-up intervals for patients at extreme risk, aiming to optimize care and minimize risks. Additionally, we recommend subsequent follow-up intervals of 6 months for this particular patient risk category, ensuring ongoing care and risk reduction and earlier if dose adjustments were done.

During follow-up, a full lipid profile should be performed. Additionally, non-HDL-C or ApoB should also be analyzed and used as a secondary treatment target. Adherence to both medication and lifestyle regimens is crucial for maximizing the reduction of ASCVD risk. 29, 51

Non-statin uses in special populations

Diabetes

The use of statins in diabetic patients in the primary prevention trials has shown significant CV outcome benefit, thus all diabetic patients aged from 40 to 75, and having no contraindications, will benefit from at least moderate-intensity statins, whereas higher-risk diabetic patients (e.g., older patients, patients with additional risk factors, albuminuria, retinopathy, long-standing DM, CKD or any sort of diabetic nephropathy) would probably benefit from high-intensity statins.

The target LDL level depends upon the risk stratification of the patient based on ASCVD, severe TOD or SCORE2-Diabetes. The first line should be statins; however, if the target LDL was not achieved on the maximally tolerated statin dose, the physician should share a decision-making involving the patient on using another non-statin therapy.

The initial non-statin therapy should be ezetimibe 10 mg daily dose. According to the writing committee, bempedoic acid and/or PCSK9-targeted therapy can be considered if patients have an inadequate response to statin/ezetimibe or if patients are statin-intolerant. Inclisiran has currently no established evidence-based role for primary prevention of ASCVD in patients with diabetes; however, it can be considered if patients do not reach their targets on statin/ezetimibe combination in very high- or extreme-risk patients. 70

Chronic kidney disease

Although many of the initial statin CVD studies did not include many CKD patients, evidence from subgroup analyses of large statin studies suggested that CKD subjects had similar benefits to non-CKD individuals 13, 14. Furthermore, for CKD patients with pre-end-stage renal disease, statins effectively lower total cholesterol and LDL cholesterol levels and decrease CVD risk. However, the benefit of statins is unclear in patients with nephrotic syndrome and was absent in patients with only microalbuminuria 15 and those on regular hemodialysis.

Fibrates are known to decrease renal blood flow and glomerular filtration, and they are cleared renally; therefore, there is significant concern regarding their use in CKD.

Ezetimibe is metabolized through intestinal and hepatic metabolism, and does not require any dose adjustment in CKD or ESRD, making it potentially attractive therapy in CKD.

A secondary analysis from the IMPROVE IT trial evaluating outcomes based on eGFR shows that compared to statin alone, the combination of statin + ezetimibe was more effective in reducing risk of CVD outcomes in those with eGFR < 60/ml/min/1.73 m². 16

The effects of evolocumab treatment on LDL lowering were similar in the normal renal function group and the renally impaired groups, with no clinically important adverse events 18. Regarding alirocumab, a subgroup analysis from Odyssey Outcomes Trial, showed it to be safe down to GFR of 30, but for GFR less than 30, there are no available data. 19

Bempedoic acid use in CKD is approved without dosage adjustment for eGFR > 30 ml/minute/1.73 m². As bempedoic acid has hepatic metabolism, it is presumably safe in CKD.

Regarding inclisiran, there is no recommended dosage adjustment in CKD, but there have been no studies done in patients with ESRD. An analysis of the ORION-1 and ORION-7 studies compared inclisiran in patients with renal impairment and those with normal renal function, and found similar safety and efficacy, suggesting that no dose adjustment is needed in CKD. However, no patients on dialysis were studied in these trials.

Heart failure

Statin use in HF

The use of statins in patients with symptomatic heart failure with reduced EF was addressed in two trials (CORONA and GISSI-HF), both trials did not show significant reductions in primary endpoints; however, a subsequent meta-analysis of these trials demonstrated

a significant 19% reduction in MI rates among patients with ischemic etiology of heart failure; therefore, the writing committee of this consensus states that it is reasonable to consider the use of statins in patients with symptomatic heart failure due to ischemic etiology or in the presence of dyslipidemia necessitating treatment. [71–73]

Ezetimibe use in HF

A post hoc analysis of IMPROVE-IT predicted the greatest likelihood from adding of ezetimibe to statin therapy following ACS in heart failure subgroup 42; therefore, the writing committee of this consensus recommends that for patients with ASCVD and a history of heart failure who achieve inadequate lowering of LDL-C on maximally tolerated statin therapy, the addition of ezetimibe may be reasonable.

PCSK9 use in HF

Alirocumab failed to reduce MACE in HF patients in a post hoc analysis and was associated with increase in non-fatal MI. Based on this, the writing committee of this consensus judges that no recommendations can be made in this regard, and the patients with ASCVD and NYHA II–III HF due to ischemic etiology should follow the algorithm for patients with ASCVD at very high-risk on statin therapy for secondary prevention.

Inclisiran and bempedoic acid use in HF

Inclisiran trials 74 have excluded patients with HF NYHA classes II, III, and IV and patients with LVEF < 30%. Also, the CLEAR-OUTCOMES trial of bempedoic acid excluded patients with severe heart failure. Therefore, the writing committee of this consensus judges that no recommendations can be made in this regard.

Women considering pregnancy or already pregnant Statin use

Until 2021, the use of statins in pregnancy was absolutely contraindicated. However, in July 2021, the FDA requested revisions to the information regarding use of statins in pregnancy, removing the contraindication against use in all pregnant patients 75. However, the writing committee of this consensus does not recommend the use of statins in pregnant or breastfeeding mothers pending further safety information. Referral to a lipid specialist for high-risk patients including homozygous familial hypercholesterolemia and those who have clinical ASCVD is advised. We also recommend to stop statins for at least 2 months before planned pregnancy and to refer those at elevated risk to a lipid specialist.

Ezetimibe/bempedoic acid/inclisiran/PCSK9

There are no well-controlled trials for the use of these drugs during pregnancy; therefore, the writing committee of this consensus stated that no recommendation can be made in this regard.

Elderly

Few studies have focused on lowering LDL-C in elderly patients (≥ 75 years). The PROSPER Trial investigated the effect of pravastatin ($n=2891$) versus placebo ($n=2913$) on CV events in older subjects, statins lowered LDL-C by 34% compared to the placebo group and reduced the primary end point by 15% in patients with preexisting CVD. However, the study failed to demonstrate the benefit of statins in the elderly without CVD 76. According to the writing committee, the initial non-statin therapy should be ezetimibe 10 mg daily dose. Bempedoic acid and/or PCSK9-targeted therapy can be considered if patients have an inadequate response to statin/ezetimibe or if patients are statin-intolerant.

Familial hypercholesterolemia

The previous studies have reported that only a minority of the FH patients reached their LDL-C target. The main determinants associated with reaching the LDL-C target were a lower LDL-C before treatment and treatment with a PCSK9-I. 77

In HeFH, both alirocumab and evolocumab have been tested. In the Rutherford-2 trial, evolocumab lowered LDL-C by 60%, non-HDL-C by 56%, apolipoprotein B by 49%, Lp(a) by 31% and triglycerides by 22% while increasing HDL by 8% 78. In the Odyssey FH I and FH II studies, alirocumab lowered LDL-C by approximately 55%, non-HDL-C by ~50%, apolipoprotein B by ~43%, Lp(a) by ~19% and TG by ~14% while increasing HDL by ~7% 79. Thus, in these difficult to treat patients, PCSK9 monoclonal antibodies were still very effective at lowering pro-atherogenic lipoproteins.

In HoFH, evolocumab resulted in a 21–31% decrease in LDL-C compared to placebo in patients with homozygous FH 80, 81. The response to treatment seems to be dependent on the primary genetic cause. Patients with mutations in the LDL receptor leading to the expression of defective receptors respond to therapy whereas patients with mutations leading to negative receptors (null variants) have a poor response. The mechanism by which PCSK9 inhibitors lower LDL-C levels is not surprising, as patients that do not have any functional LDL receptors will not respond to therapy. Alirocumab decreased LDL-C by 35.6%, non-HDL-C by 32.9%, apolipoprotein B by 29.8% and Lp (a) by 28.4% (84,85). Given that PCSK9 monoclonal antibodies

decrease LDL-C levels in some FH patients, these drugs can be useful in this very difficult-to-treat patient population. [80–83

Patients with statin-associated side effects

The most-encountered statin-associated side effects (SASEs) in clinical practice is statin-associated muscle symptoms, which may occur in 5–20% of patients; however, true complete intolerance is actually rare [84]. For patients with SASEs who meet evidence-based guideline criteria for statin therapy, avoiding complete discontinuation of statin treatment is recommended whenever possible. In the SAMSON (Self-Assessment Method for Statin Side effects Or Nocebo) trial of patients who discontinued a statin due to SASEs, 90% of the adverse symptom effects experienced with drug therapy can be attributed to what is seen with a blinded placebo. [85

Although there is no universally accepted definition of statin intolerance, most experts recommend that patients are documented to have unacceptable muscle-related symptoms that resolve with discontinuation of therapy and recur with rechallenge on at least two (and preferably 3) statins, preferably ones that are metabolized by different pathways and have different lipophilicity/hydrophilicity, and one of which is prescribed at the lowest approved dose. Non-statin therapies can help manage dyslipidemia in such patients who have statin intolerance. [86

A trial of bempedoic acid + ezetimibe may be considered as first-line non-statin therapy in such patients. As an alternative, PCSK9 monoclonal antibodies ± ezetimibe may be considered depending on the patient's clinical scenario. Inclisiran may also be considered especially in patients who are not compliant to treatment. [86

Conclusions

This consensus statement emphasizes key recommendations on the use of non-statin therapies in the management of cardiovascular disease (CVD). We highlight the importance of identifying patients at extreme CV risk, which allows for targeted interventions and personalized treatments. We believe that statins will no longer stand alone in the battle against atherosclerosis. Furthermore, we propose considering initial combination therapy for individuals at very high and extreme risk, and suggest expanded use of bempedoic acid in patients who are still not at LDL-C goal on statin/ezetimibe combination especially in resource-limited settings as well as in statin-intolerant patients. These recommendations aim to optimize treatment strategies and enhance

patient outcomes. However, further research and real-world data are necessary to validate and refine the implementation of these recommendations.

Abbreviations

ACL	ATP citrate lyase
ACS	Acute coronary syndrome
ANGPTL3	Angiotensin-like protein 3
ASCVD	Atherosclerotic cardiovascular disease
AUs	Agatston units
CABG	Coronary artery bypass surgery
CAC	Coronary artery calcium
CHD	Coronary heart disease
CHF	Congestive heart failure
CKD	Chronic kidney disease
CV	Cardiovascular
CVD	Cardiovascular diseases
DM	Diabetes mellitus
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
GBD	Global Burden of Disease
HDL	High-density lipoprotein
HeFH	Heterozygous familial hypercholesterolemia
HMG-CoA	Hydroxymethylglutaryl-coenzyme A
HoFH	Homozygous familial hypercholesterolemia
HTN	Hypertension
LDL-C	Low-density lipoprotein cholesterol
LLT	Lipid-lowering therapies
Lp (a)	Lipoprotein (a)
MACCE	Major adverse cardiovascular events
MI	Myocardial infarction
MTP	Microsomal triglyceride transfer protein
NPC1L1	Niemann–Pick C1-Like-1
PAD	Peripheral arterial disease
PCEs	Pooled cohort equations
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
RCTs	Randomized controlled trials
SASEs	Statin-associated side effects
siRNA	Small interfering RNA
TG	Triglyceride
TOD	Target organ damage

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"All authors have read and approved the manuscript." HS was the main author, put the idea behind this review and wrote and approved the final manuscript. HKa contributed to the writing of this manuscript and has read and approved the final manuscript. HM contributed to the writing of this manuscript and has read and approved the final manuscript. NF contributed to the writing of this manuscript and has read and approved the final manuscript. HKh contributed to the writing of this manuscript and has read and approved the final manuscript. GN contributed to the writing of this manuscript and has read and approved the final manuscript. MS contributed to the writing of this manuscript and has read and approved the final manuscript. MAbd contributed to the writing of this manuscript and has read and approved the final manuscript. MAbo contributed to the writing of this manuscript and has read and approved the final manuscript. MM contributed to the writing and editing of this manuscript and has read and approved the final manuscript.

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Declarations

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