Drugs
https://doi.org/10.1007/s40265-024-02105-5

REVIEW ARTICLE

2024 Recommendations on the Optimal Use of Lipid-Lowering Therapy in Established Atherosclerotic Cardiovascular Disease and Following Acute Coronary Syndromes: A Position Paper of the International Lipid Expert Panel (ILEP)

Maciej Banach · Željko Reiner · Stanisław Surma · Gani Bajraktari · Agata Bielecka-Dabrowa · Matjaz Bunc, et al. ***[full author details at the end of the article]***

Accepted: 30 September 2024

Abstract
Atherosclerotic cardiovascular disease (ASCVD) and consequent acute coronary syndromes (ACS) are substantial contributors to morbidity and mortality across Europe. Fortunately, as much as two thirds of this disease's burden is modifiable, in particular by lipid-lowering therapy (LLT). Current guidelines are based on the sound premise that, with respect to low-density lipoprotein cholesterol (LDL-C), "lower is better for longer", and recent data have strongly emphasised the need for also "the earlier the better". In addition to statins, which have been available for several decades, ezetimibe, bempedoic acid (also as fixed dose combinations), and modulators of proprotein convertase subtilisin/kexin type 9 (PCSK9 inhibitors and inclisiran) are additionally very effective approaches to LLT, especially for those at very high and extremely high cardiovascular risk. In real life, however, clinical practice goals are still not met in a substantial proportion of patients (even in 70%). However, with the options we have available, we should render lipid disorders a rare disease. In April 2021, the International Lipid Expert Panel (ILEP) published its first position paper on the optimal use of LLT in post-ACS patients, which complemented the existing guidelines on the management of lipids in patients following ACS, which defined a group of "extremely high-risk" individuals and outlined scenarios where upfront combination therapy should be considered to improve access and adherence to LLT and, consequently, the therapy's effectiveness. These updated recommendations build on the previous work, considering developments in the evidential underpinning of combination LLT, ongoing education on the role of lipid disorder therapy, and changes in the availability of lipid-lowering drugs. Our aim is to provide a guide to address this unmet clinical need, to provide clear practical advice, whilst acknowledging the need for patient-centred care, and accounting for often large differences in the availability of LLTs between countries.

1 Introduction

1.1 Background and Context

Atherosclerotic cardiovascular disease (ASCVD) results in myocardial ischaemia and is the largest contributor to morbidity and mortality across Europe and worldwide [1, 2]. In 2017, almost 35 million people were estimated to live with ischaemic heart disease (IHD) in 54 European Society of Cardiology (ESC) member countries, resulting in an estimated cost of €59 billion in 2015 [3]. The Global Burden of Disease (GBD) study estimated a prevalence of over 315 million cases of IHD in 2022, contributing to over 9 million deaths and an age-standardised rate of loss of 2275 disability adjusted life years (DALYs) per 100,000 people [2]. The same report indicated that 4.5 million deaths per year are attributable entirely to low-density lipoprotein (LDL) cholesterol (LDL-C) [2]. In ESC member countries, the median number of age-standardised DALYs due to cardiovascular disease (CVD) was 4530 per 100,000 inhabitants, of which 54% were attributable to IHD [3]. The most recent GBD analysis on the global burden of 288 causes of death and life expectancy reduction in 204 countries and territories in the years 1990–2021 showed that IHD was the most common cause of death in 2021 (108.7/100,000), with coronavirus

Maciej Banach and Peter E. Penson contributed equally to the preparation of the paper.

Published online: 04 November 2024

Key Points

Despite new knowledge, approaches, and drugs, there are still four out of five very high- and extremely high-risk patients not achieving their low-density lipoprotein cholesterol goal of therapy, which significantly increases the risk of first and recurrent cardiovascular disease (CVD) events and mortality.

New 2024 International Lipid Expert Panel (ILEP) recommendations, based on the most recent available data, prompt on how to increase the effectiveness of therapy in very high-risk secondary prevention patients with upfront lipid-lowering combination therapy – double or even triple in the case of extremely high-CVD-risk patients.

The recommendations also present the justification and guidance on upfront lipid-lowering combination therapy in patients with established pre-event atherosclerotic CVD, and in specific populations of patients with metabolic disorders and statin intolerance.

disease 2019 (COVID-19) in second place (94.0/100,000), and stroke in third place (87.4/100,000) – clearly indicating that two out of three main causes of death are due to atherosclerosis [4]. The European Association of Percutaneous Cardiovascular Interventions (EAPCI) have reported an annual median of 2478 percutaneous coronary intervention (PCI) procedures per million people [5]. It is important to emphasise that most of this disease burden is modifiable, in particular, by effective lipid-lowering therapy (LLT) [6, 7]. In addition to statins and ezetimibe (ideally as a fixed dose combination [FDC]), bempedoic acid [8, 9] and monoclonal antibody/small interference RNA (siRNA) targeting [10] proprotein convertase subtilisin/kexin type 9 (PCSK9) present an additional opportunity to significantly reduce LDL-C levels (by even > 85%) and consequently reduce the risk of ASCVD. These new agents are more expensive than other LLTs and, therefore, should be prioritised for use in those patients who are most likely to benefit from them. These are patients at very high risk of ASCVD, including those with familial hypercholesterolaemia (FH), those with an ASCVD pre-event, and those who have already experienced an acute coronary syndrome (ACS) [11, 12].

Multiple sources of evidence demonstrate that an individual's lifetime exposure to LDL-C determines their risk of ASCVD [6, 13]. This is also a reason that it seems we are closer and closer to replacing 5- to 10-year risk scores with the estimations of lifetime CVD risk [14]. In patients at high CVD risk and especially in those who have had a myocardial infarction (MI), poor adherence to statin therapy is common, and is associated with worse outcomes [15, 16], attainment of treatment targets is poor [17], even despite the fact that higher-intensity LLT results in fewer ASCVD events than less-intensive treatment [18, 19]. Whilst primary prevention uses prediction tools such as the Systematic COronary Risk Evaluation (SCORE2 or SCORE2-OP or SCORE-2-Diabetes) to grade risk, ASCVD and post-ACS patients are categorised as "very high risk" in current ESC/European Atherosclerosis Society (EAS) dyslipidaemia guidelines [20–22], although they are in fact a heterogeneous group, in which risk factors can be used to identify those individuals at extreme risk of further ASCVD events [23]. Those individuals with the highest absolute risk are likely to receive the largest benefit from innovative treatment with PCSK9 inhibitors (PCSK9Is), bempedoic acid, and inclisiran [7, 8].

In view of the urgent need to ensure that guideline-directed LLT is prescribed to all ASCVD/ACS patients to ensure those individuals at greatest risk of recurrent events can access the most efficacious LLT without delay, thereby reducing their exposure to elevated LDL-C, the ILEP developed a position paper in April 2021 [24]. This position paper complemented the existing guidelines on the management of lipids in patients following ACS, defined a group of "extremely high-risk" individuals, and, for the first time, outlined scenarios where upfront combination therapy should be considered to improve access and adherence to LLT. This updated 2024 position paper builds on the previous work, considering the substantial developments in the evidential underpinning of combination LLT and changes in the availability of lipid-lowering drugs.

Our aim is to provide a guide to address this unmet clinical need, to provide clear practical advice, whilst acknowledging the need for patient-centred care, and accounting for ongoing large differences in the availability of LLTs between countries.

1.2 Organisation of the Position Paper

The members of the Writing Committee (WC) who prepared these recommendations were selected by the ILEP Steering Committee from the experts who worked on the previous version of the document (which was a part of the ACS EuroPath Central and South European Countries Project) plus additional recognised experts in the field who were not necessarily ILEP members (scientific experts and/or those with a large base of practical experience). The WC (led by Prof. Maciej Banach and Prof. Peter Penson) carried out an extensive review of the published scientific evidence on the presented subject as well as a critical evaluation of the therapeutic procedures, including risk–benefit assessment. The content of the paper and suggested recommendations

were discussed with the WC members multiple times during online and onsite meetings (including the official ILEP meeting during the ESC 2023 in Amsterdam). Every co-author had a chance to discuss, review extensively, revise, and approve the final version of the recommendations. The WC followed the ILEP policy (https://ilep.eu/publications/) while working on this paper. In the process of suitable data searching for this paper, the GRADE approach was applied. This position paper is a supplemented version of the recommendations first published in this form in April 2021 [24]. The experts from the teams that developed and peer-reviewed the guidelines completed the conflict-of-interest forms with regard to all relationships that might be perceived as actual or potential sources of conflicts of interest.

Cardiologists, lipidologists, diabetologists, and physicians of various specialties who deal with high-risk patients with lipid disorders are encouraged to consider these guidelines when conducting clinical assessments, as well as defining and implementing medical prevention, diagnosis, or treatment strategies. Nevertheless, the guidelines in no way absolve physicians from individual responsibility for making correct and accurate decisions, considering the patient's health status and in consultation with the patient and, if necessary, with his/her caregiver. Healthcare professionals are responsible for verification of policies and regulations pertaining to medicines and devices in effect at the time of their prescription and/or use.

1.3 Major Updates Since 2021 ILEP Position Paper

1.3.1 International Guidelines and ILEP Position Papers

Since the publication of the 2021 position paper on optimal management of lipids in ACS [24], a number of additional guidelines and consensus and position papers have been published. These include, among others, the 2021 ESC guidelines on prevention of CVD [21], the expert opinion paper on the upfront lipid-lowering combination therapy [25], and the 2023 ESC guidelines on ACS management [20]. The International Lipid Expert Panel (ILEP) has published relevant position papers on the management of the nocebo/drucebo effect in statin therapy [26], the use of bempedoic acid in CVD risk reduction [8] (plus an updated review on this [27]), and the management of dyslipidaemia in individuals with diabetes [28]. The recent Polish Lipid Association (PoLA) guidelines on the place of pitavastatin and elevated lipoprotein(a) [Lp(a)] diagnosis and therapy were also important in creating these recommendations [29, 30]. Additionally, large cohort studies on the role of upfront lipid-lowering combination therapy in the reduction of CVD endpoints and all-cause mortality [19, 31] and an influential ILEP viewpoint on the upfront use of combination therapy have strongly supported the use of this approach in high-risk patients [32]. These are discussed, where relevant, in the sections below.

1.3.2 Continued Poor Attainment of Lipid-Lowering Targets

Despite the undoubted benefit of LLT in the prevention of CVD, attainment of treatment targets continues to be highly disappointing, highlighting the need for more intensive LLT. In 2021, results from the DA VINCI study in Europe indicated that only 17% of very high-risk primary-prevention patients and 22% in secondary prevention met their LDL targets according to the 2019 European guidelines, with much worse results for Central and Eastern European (CEE) countries, where only 13% of very high-risk patients in secondary prevention met the LDL-C target of < 55 mg/dL (1.4 mmol/L) [33, 34]. More recently, the SANTORINI study highlighted treatment gaps in the implementation of LDL-C control among high- and very high-risk patients in Europe between 2020 and 2021 [17]. The study involved adults at high- or very high-risk of CVD (unfortunately, only from the Western countries) and found that 22% were receiving no LLT at all, and only 20% of patients reached the goals outlined in the 2019 guidelines [17]. This is consistent with older evidence suggesting the median time to discontinuation after the initiation of statin therapy is 15 months [35]. An encouraging observation of this study was an increased number of patients on the lipid-lowering combination therapy (up to 50% in some of the countries) [17]. This is also in line with the observations from other countries, where, after the 2021 ILEP recommendations and other experts' papers, the number of patients on (upfront) lipid-lowering combination therapy significantly increased [36]. In Poland, which is the sixth largest European country, the number of sold medicine packages of statins and ezetimibe (as FDC) increased tenfold in comparison to the 2020–2021 period (IMS data, April 2024). At the same time, however, it was noticed that as many as 24% of physicians reduced the dose of statin while starting ezetimibe, decreasing the expected positive effect of the intensive lipid-lowering combination therapy [36]. Thus, we should always underline that, for high-risk patients, we should apply lipid-lowering combination therapy with a high-intensive statin (if tolerated) and ezetimibe.

1.3.3 Outcomes Data Supporting Upfront Combination Therapy

The previous ILEP position paper [24] based its recommendations on clinical evidence, in addition to the unarguable relationship between LDL-C and cardiovascular events. Since the publication of the position paper, further clinical evidence has emerged to support the use of upfront

lipid-lowering combination therapy in high-risk patients to prevent cardiovascular events. The multicentre RACING trial, conducted in South Korea, recruited 3780 ASCVD patients, of whom 2497 had prior PCI. Patients were randomised to receive either moderate-intensity statin with ezetimibe combination therapy (rosuvastatin 10 mg with ezetimibe 10 mg) or high-intensity statin monotherapy (rosuvastatin 20 mg) and were followed up for 3 years for major adverse cardiovascular events (MACE) outcomes. Combination therapy was found to be non-inferior to high-intensity statin treatment (HR 0.95; 95% Confidence Interval [CI] 0.74–1.24; $p = 0.781$), despite it being associated with significantly more patients on LDL-C goal and significantly fewer side effects and discontinuations (better therapy adherence) [37]. The same results were next observed in the post hoc analyses in the challengeable group of patients with diabetes or in older adults [38, 39].

These trial data are complemented by real-world evidence (RWE) from the PL-ACS registry based on the data of 38,023 consecutive patients with ACS who were discharged alive, for which propensity-score matching was used to compare the outcomes of patients treated with statin monotherapy (atorvastatin or rosuvastatin; $n = 768$) or upfront combination therapy of statin and ezetimibe ($n = 768$ patients). Patients treated with upfront combination therapy had a significantly reduced risk of all-cause mortality between groups after 1 year (5.9% vs 3.5%; $p = 0.041$), 2 years (7.8% vs 4.3%; $p = 0.019$), and 3 years (10.2% vs 5.5%; $p = 0.024$) of follow-up (with a 4.7% absolute risk reduction after 3 years and a number needed to treat [NNT] of 21) [31]. Moreover, the significant benefit for prolonged survival was observed already after 52 days after therapy initiation [31].

Similar results were observed in two RWE analyses based on the RACING study inclusion criteria. Based on the 72,050 patients' data from the Drug Eluting Stent (DES) Registry from South Korea, the authors investigated the effect of the upfront lipid-lowering combination therapy on the primary endpoint, which was the 3-year composite event of CVD death, MI, coronary artery revascularisation, hospitalisation for heart failure (HF), or nonfatal stroke [19]. They showed that combination LLT was associated with a lower occurrence of the primary endpoint (11.6% vs 15.2%; HR 0.75; 95% CI 0.70–0.79; $p < 0.001$; NNT = 28), with fewer discontinuations of statin treatment (6.5% vs 7.6%; HR 0.85; 95% CI 0.78–0.94; $p < 0.001$) and a lower occurrence of new-onset diabetes (NOD) requiring medication (7.7% vs 9.6%; HR 0.80; 95% CI 0.72–0.88; $p < 0.001$; NNT = 53) [19]. Based on the same registry, the beneficial effect of the upfront lipid-lowering combination therapy was observed also for the combination of atorvastatin and ezetimibe (similarly to the findings of Lewek et al. [31]). Combination LLT of atorvastatin 20 mg and ezetimibe was associated with a lower incidence of the primary endpoint (in comparison to atorvastatin 40–80 mg in monotherapy; 12.9% vs 15.1%; HR 0.81; 95% CI 0.74–0.88; $p < 0.001$; NNT = 45) and significantly lower rates of statin discontinuation (8.4% vs 10.0%; HR 0.81; 95% CI 0.73–0.90; $p < 0.001$) and NOD requiring medication (7.0% vs 8.8%; HR 0.80; 95% CI 0.70–0.92, $p = 0.002$) [40]. In the most recent meta-analysis, presented at the ESC Congress 2024 in London, Banach et al., on behalf of the ILEP and Lipid and Blood Pressure Meta-analysis Collaboration Group (LBPMC), and based on the data from 11 studies (eight randomised controlled trials [RCTs] and three cohort studies) with 106,358 patients, showed that upfront combination LLT significantly reduced LDL-C level from the baseline by 12.13 mg/dL [0.31 mmol/L] ($p < 0.001$), all-cause mortality by 25% ($p = 0.01$), cardiovascular mortality by 25% ($p < 0.001$), and MACE by 28% ($p < 0.001$), when compared with statin monotherapy alone. The therapy discontinuation rate was comparable between combination LLT and statin monotherapy groups (with numerical 13% reduction), and the risk of adverse events related to the gastrointestinal tract and musculoskeletal system was comparable between both investigated groups [41].

The concept of FDC therapy (or polypills) to improve adherence to therapeutic agents in the management of cardiovascular risk (particularly in primary prevention) has been proposed for over 2 decades [42]. Recent evidence and existing guidelines strongly support the use of FDC therapy [22, 43, 44], especially as more and more evidence supports its application to increase efficacy and improve safety/tolerability. In a real-world observational study including 311,242 patients treated with statin and ezetimibe as separate formulations, or FDCs (at the same doses), a greater reduction in LDL-C was seen in the FDC group (28.4%; 40.0 ± 39.1 mg/dL) compared to separate pills (19.4%; 27.5 ± 33.8 mg/dL), $p < 0.0001$. Furthermore, FDC therapy was associated with a greater attainment of target LDL-C levels of < 70 mg/dL/1.8 mmol/L (31.5% vs 21.0%) and < 55 mg/dL/1.4 mmol/L (11% vs 5.7%) [45].

All abovementioned observations resulted in changes in the ESC guidelines for ACS management, suggesting upfront lipid-lowering combination therapy in patients with ACS (class/level IIb B) [20]. Forthcoming RWE data and ongoing RCTs (Ez-PAVE trial [NCT04626973], ESCORT trial [NCT05782777] in ASCVD/MI patients, or CARE-PVD trial [NCT06231966] in polyvascular disease [PVD] patients) will hopefully further support the existing data and strengthen the existing recommendations.

1.3.4 Current Availability of Novel Therapeutic Agents

During the period since the publication of the 2021 position paper [24], the availability of new therapeutic agents has expanded the horizon of lipid-lowering treatments. Brief introductions to newly available agents are provided below,

with the reader directed to more detailed reviews. It is notable that access to and the availability of novel agents varies substantially between countries and regions, which significantly affects the achievement of lipid targets

1.3.4.1 Bempedoic Acid Bempedoic acid is a pro-drug (inactive in muscle) and is converted in the liver into an inhibitor (first in class) of adenosine triphosphate (ATP)-citrate-lyase (ACL), which lies upstream of 3-hydroxy-3-methylglutaryl-(HMG)-coenzyme A reductase (the target of statins) in the mevalonate pathway of cholesterol biosynthesis [27, 46]. In addition to LDL-C lowering, phase 3 data showed its favourable effects on inflammatory markers (high sensitivity C-reactive protein [hsCRP]) and plasma glucose/hemoglobin A1c [HbA1c] [8]. The CLEAR Outcomes trial was the first interventional CVD outcomes trial in statin-intolerant patients who had or were at high risk for CVD. The patients were assigned to receive oral bempedoic acid, 180 mg daily, or placebo. The primary endpoint was a four-component composite of MACE, defined as death from cardiovascular causes, nonfatal MI, nonfatal stroke, or coronary revascularisation [47]. A total of 13,970 patients were finally included, the mean age was 65.5 years, there were 48% females, and the median duration of follow-up was 40.6 months. The mean LDL-C reduction of 21.1% (difference between groups) was associated with the significant reduction of a primary endpoint (in comparison to placebo, 11.7% vs 13.3%; HR 0.87; 95% CI 0.79–0.96; $p = 0.004$; NNT = 63), the composite of death from cardiovascular causes, nonfatal stroke, or nonfatal MI (8.2% vs 9.5%; HR 0.85; 95% CI 0.76–0.96; $p = 0.006$), fatal or nonfatal MI (3.7% vs 4.8%; HR 0.77; 95% CI 0.66–0.91; $p = 0.002$), and coronary revascularisation (6.2% vs 7.6%; HR 0.81; 95% CI 0.72–0.92; $p = 0.001$). The incidences of gout and cholelithiasis were higher with bempedoic acid than with placebo (3.1% vs 2.1% and 2.2% vs 1.2%, respectively), as were the incidences of small increases in serum creatinine, uric acid, and hepatic enzyme levels; none of those adverse events seems to have any clinical relevance [47]. The subanalysis also confirmed its benefits in pre-diabetic and diabetic populations (45.6% patients with diabetes, 41.5% with pre-diabetes, 12.9% with normoglycaemia). Patients with diabetes who were treated with bempedoic acid had significant reductions in MACE (HR 0.83; 95% CI 0.72–0.95) compared to placebo [9]. Importantly, while bempedoic acid did not confirm its reduction potential in relation to NOD as it was in phase 3 studies [48], it confirmed that the therapy is not associated with any risk of developing NOD (HR 0.95; 95% CI 0.83–1.09; with an all-together 3% absolute reduction of NOD), and had slight optimisation of fasting blood glucose (FBG) and HbA1c [8, 9, 49]. Other sub-analyses revealed its significant potential to reduce subsequent and total CVD events [50] and a large benefit related to hsCRP reduction (by even > 40% in phase 3 trials [51] and 21.6% placebo corrected in the CLEAR Outcomes trial [48]), and compared with placebo, bempedoic acid had similar efficacy for reducing CVD risk across hsCRP and LDL-C strata [52]. The CLEAR Outcomes trial also confirmed significant efficacy of bempedoic acid in high-risk primary-prevention patients ($n = 4206$) [53]. A significant reduction of the primary endpoint was observed (5.3% vs 7.6%; adjusted Hazard Ratio [aHR] 0.70; 95% CI 0.55–0.89; $p = 0.002$; NNT = 43) as well as the composite of cardiovascular death, MI, or stroke (HR 0.64; 95% CI 0.48–0.84; $p < 0.001$), MI (HR 0.61; 95% CI 0.39–0.98), CVD death (HR 0.61; 95% CI 0.41–0.92), and all-cause mortality (HR 0.73; 95% CI 0.54–0.98) [53].

Bempedoic acid is available as a monotherapy or as a FDC with ezetimibe. ILEP has recently published a position paper on the use of bempedoic acid that was simultaneously published with the results of the CLEAR Outcomes study [8] with its recent update [27], and suggested that bempedoic acid may be a very useful agent in statin intolerance, or as an add-on to statin therapy in very high-risk patients when LDL-C targets are not met (see Sect. 6 for the details on recommendations). When choosing between bempedoic acid and PCSK9I as add-on therapy, reimbursement criteria and local availability (unfortunately bempedoic acid is still not available in many European countries, including CEE ones) are likely to affect decision making. Next CLEAR Outcomes sub-analyses and RWE data will be useful to confirm the efficacy and safety of bempedoic acid.

The Panel of this position paper approves the recommendations presented in the previous ILEP documents on the place of bempedoic acid in lipid-lowering management [8, 27].

1.3.4.2 Pitavastatin For many years, pitavastatin was mainly available in Japan, South Korea, India, some European countries, and the United States of America (USA). Since it became generic (2020), the drug has finally become available in many European countries, necessitating practical guidelines on how to apply it.

Pitavastatin is a potent inhibitor of HMG-coenzyme A reductase and reduces LDL-C effectively in the same way as other drugs in the class (by a mean of 43–47%, which positions it between high-intense and moderate-intense statins) [54, 55]. Uniquely, pitavastatin has some pleiotropic effects, which may be particularly beneficial in specific patient groups [56]. In particular, as a result of inhibiting of phosphatidylinositol 3-kinase (PI3K), pitavastatin does not share the propensity of other statin agents to cause a small elevation in plasma glucose and increased NOD risk (in fact, it may significantly reduce this risk, as well as improving FBG and HbA1c in comparison to other potent statins) [54]. The potential for pitavastatin to improve plasma glucose

profiles has led members of ILEP to recommend this drug as a rational treatment choice in patients with metabolic disturbances, diabetes/risk of diabetes, and pre-diabetes [28].

In 2023, the PoLA endorsed a position paper of the Polish Expert Group on the use of pitavastatin in the treatment of lipid disorders in Poland, which is of relevance in other countries where this drug is available [54]. The experts suggested the drug's essential role in the personalisation of therapy not only in patients with the risk of diabetes, but also in those with statin intolerance (the prevalence of pitavastatin intolerance is similar to placebo), in patients with HIV, and those with elevated Lp(a) levels (it seems it does not further increase Lp(a), opposite to other statins) [54]. These properties were confirmed in the recent REPRIVE trial in 7769 participants with HIV infection with a low-to-moderate CVD risk who were receiving antiretroviral therapy and pitavastatin calcium 4 mg or placebo [57]. After a follow-up of 5.1 years, the incidence of MACE was 4.81/1000 person-years in the pitavastatin group and 7.32/1000 person-years in the placebo group (HR 0.65; 95% CI 0.48–0.90; $p = 0.002$). Muscle-related symptoms occurred in 2.3% in the pitavastatin group and in 1.4% in the placebo group; diabetes mellitus occurred in 5.3% and 4.0%, respectively (there was no apparent treatment effect on glucose levels) [57]. A recent substudy also revealed that the mean noncalcified plaque volume decreased with pitavastatin when compared with placebo (mean [standard deviation, SD] change − 1.7 vs 2.6 mm^3; baseline adjusted difference − 4.3 mm^3; 95% CI − 8.6 to − 0.1; $p = 0.04$), and progression of noncalcified plaque was 33% less likely with pitavastatin when compared with placebo (relative risk 0.67; 95% CI 0.52–0.88; $p = 0.003$) [58].

These recommendations can be considered in light of the recent results of the Cholesterol Treatment Trialists' Collaboration meta-analysis of over 25,000 participants in large statin trials. It was observed that statins dose-dependently increase the number of NOD. Most NOD cases were seen in individuals who already had glycaemic markers close to the diagnostic threshold for diabetes. Whilst the authors conclude that the theoretical adverse effects of statins on cardiovascular risk that might arise from these small increases in glycaemia are already accounted for in the clearly demonstrated overall reduction in cardiovascular risk, nevertheless, even greater benefit may be observed through the use of pitavastatin in patients with elevated plasma glucose [54, 59]. It seems, therefore, that pitavastatin, as a part of therapy individualisation, should be recommended in monotherapy or as a part of LLT combination therapy with ezetimibe in patients with metabolic disturbances to increase the chance to be on LDL-C target, to improve adherence (by reducing the risk of statin-associated muscle symptoms [SAMS]), and especially to reduce the risk of NOD [54] (see Sect. 6 for details on recommendations).

Thus, the Panel of this position paper approves the recommendations presented in the recent ILEP [28] and recent PoLA guidelines [54] on the place of pitavastatin in lipid-lowering management.

1.3.4.3 Inclisiran Unlike the monoclonal antibody PCSK9I drugs (alirocumab and evolocumab), which bind to and inactivate PCSK9, inclisiran is an siRNA and interferes with the translation of PCSK9 mRNA, resulting in very long-lasting knockdown of the molecule [10]. As an add-on to the previous ORION 9–11 data (44.3–53.8% LDL-C reduction, with 19% in ORION 9 for FH patients to 61.8% in ORION 10 for ASCVD patients being on LDL-C target < 50 mg/dL [1.3 mmol/L]) [60], the ORION 3 study has demonstrated extremely promising results with this agent, which can be administered as a twice-yearly injection. Efficacy and safety have been demonstrated over 4 years. The 4-year mean reduction of LDL-C was 44.2% (95% CI 47.1–41.4), and the main adverse effect was injection-site reaction [61]. Efficacy was also confirmed in the ORION 8 study, where the inclisiran therapy was associated with a mean 49.4% LDL-C reduction, and the prespecified LDL-C goal was achieved in 78.4% of patients at the end of the study [62]. Recent data also confirmed its excellent safety profile. The post hoc analysis of completed (ORION 1, 3, 5, 9, 10, and 11) and ongoing (ORION 8) trials with 3576 patients treated with inclisiran for up to 6 years and 1968 patients treated with placebo for up to 1.5 years showed that treatment-emergent adverse events (TEAEs) that were serious or led to discontinuation, hepatic, muscle, and kidney events, incident diabetes, and elevations of creatine kinase or creatinine occurred at a comparable rate between groups for up to 1.5 years, with similar trends continuing for inclisiran beyond this period. Treatment-induced antidrug antibodies were uncommon with inclisiran (4.6%), with few of them persistent (1.4%), and were not associated with a greater incidence of TEAEs leading to study drug discontinuation or serious TEAEs [63].

Very interesting results were presented at the ACC (American College of Cardiology) Scientific Sessions 2024 in Atlanta based on the completed VICTORION-Initiate study, which aimed to evaluate the effectiveness of an "inclisiran first" implementation strategy by adding inclisiran immediately upon failure to reach LDL-C < 70 mg/dL (1.8 mmol/L) despite receiving maximally tolerated statins, in comparison to standard care in US patients with ASCVD [64]. A total of 450 patients (30.9% female) with mean baseline LDL-C of 97.4 mg/dL were randomised. The "inclisiran first" strategy led to significantly greater reductions in LDL-C from baseline to day 330 versus usual care (60.0% vs 7.0%; $p < 0.001$), with more patients achieving LDL-C goals (< 70 mg/dL: 81.8% vs 22.2%; < 55 mg/dL: 71.6% vs 8.9%; $p < 0.001$, respectively). Statin discontinuation rates

with "inclisiran first" (6.0%) were noninferior versus usual care (16.7%) [64].

Based on the data from the ORION 9–11 studies, we have also the first results on possible CVD outcomes reduction with inclisiran. The authors showed that with a follow-up of 18 months, inclisiran significantly reduced composite MACE (odds ratio [OR] 0.74; 95% CI 0.58–0.94), but not fatal and non-fatal MIs (0.80, 0.50–1.27) or fatal and non-fatal stroke (0.86, 0.41–1.81) [65]. We still need to wait for the results of the ORION 4 trial (recruitment was completed on 30 September 2023, and the results are to be released in 2026) and VICTORION-1 (estimated study completion date: April 2029) and VICTORION-2 PREVENT (estimated study completion date: October 2027) to confirm the efficacy of inclisiran in the reduction of cardiovascular events [60].

Clearly, the infrequent need for dosing of this agent has the potential to substantially improve adherence to LLT, which again allows for therapy personalisation. Inclisiran is already available in most of the European countries, with different availability—from commercial to different forms of reimbursement (see Sect. 6 for the details on recommendations).

1.3.5 Statin Intolerance

Despite extensive data suggesting the widespread tolerability of statin therapy, statin intolerance, mostly in the form of SAMS, is the most common reason for statin non-adherence, which significantly increases the CVD risk [15, 16]. A recent meta-analysis including 4.2 million patients has demonstrated that statin intolerance prevalence is only 9.1%, which means that 91% of patients can be treated without any safety concern, and when statin intolerance is diagnosed using objective criteria, its prevalence is between 5.9% and 7% [66]. Moreover, complete statin intolerance (where the patient cannot use any dose of any statin) is even lower, with a prevalence of < 3% [67, 68]. This gives confidence in using statin therapy as the mainstay of treatment in most ASCVD patients. Furthermore, the meta-analysis has allowed the identification of factors most associated with statin intolerance (age, OR 1.33, $p = 0.04$; female gender, OR 1.47, $p = 0.007$; Asian and Black race, $p < 0.05$ for both; obesity, OR 1.30, $p = 0.02$; diabetes mellitus, OR 1.26, $p = 0.02$; hypothyroidism, OR 1.37, $p = 0.01$; chronic liver and renal failure, $p < 0.05$ for both), allowing caution to be employed when commencing treatment in such patients [66].

The recent state-of-the-art paper also summarised the (causal) symptoms that might be expected as side effects after statin therapy, including only SAMS, NOD, and temporary elevation of liver enzymes [69]. The paper also strongly emphasised the lack of clear evidence on the causality and increased risk of haemorrhagic stroke associated with statin therapy and low to extremely low levels of LDL-C, which has been also confirmed in the recent analyses and recommendations [70–72]. Finally, recent ILEP recommendations [26], for the first time, presented the stepwise approach on how to manage patients with statin intolerance, but also how to overcome the nocebo/drucebo effect, introducing among others the personalised lipid intervention plan (PLIP) – a critically important approach, which includes tools to aid in the adequate education of patients. Altogether, after implementing these recommendations, LDL-C targets could be achieved in as many as 95% of patients with statin intolerance [73].

The Panel of this position paper approves the recent ILEP recommendations on the management of statin intolerance and the drucebo effect [26, 73].

2 Guideline Context

The use of LLT in ASCVD/ACS is covered in the 2019 ESC/EAS guidelines for the management of dyslipidaemias [22], the 2021 ESC guidelines on CVD prevention in clinical practice [21], and the 2023 ESC guidelines on management in ACS [20]. The guidelines are based on sound principles of LDL-C reduction: the earlier the better, the lower the better, the longer the better [74, 75]. The importance and benefit of early access to statin therapy and lipid-lowering combination therapy with non-statin drugs is highlighted [11, 20–22, 76]. The guidelines recommend intensification of statin therapy and addition of ezetimibe if treatment targets are not met (Class IIa) [22]. Furthermore, if the LDL-C goal is not achieved after 4–6 weeks despite maximally tolerated statin therapy and ezetimibe, addition of a PCSK9I is recommended (Class 1) [22]. These guidelines for the first time also suggested the possibility of introducing PCSK9Is for ACS patients during hospitalisation (Class IIa) [22]. The 2023 guidelines also allowed for immediate (upfront) lipid-lowering combination therapy in ACS patients (Class IIb) [20].

Nevertheless, this incremental approach of adding drugs after failing to meet targets does not allow for the fact that the proportional lipid reduction could be achievable with current treatments in real life [22], and in many cases with very high baseline LDL-C, monotherapy is extremely unlikely to enable patients to reach their treatment targets [17, 33, 34, 77, 78]. This results in delay to target attainment and unnecessary further exposure to LDL-C. Furthermore, the guidelines treat all ASCVD patients ["Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, coronary artery bypass grafting [CABG], and other arterial revascularization procedures), stroke and transient ischemic attack (TIA), and peripheral arterial disease."] as "very high

risk" without accounting for large heterogeneity and allowing for variability within this group [22]. In the 2019 ESC/EAS guidelines, an attempt to define extremely high-risk patients was made; however, this was not continued in the recent guidelines, which may also be one of the reasons only < 20% of these patients reached their LDL-C goal, resulting in a 10–20% risk of recurrent events in post-MI patients within the first 12 months [78].

In light of the above and the RWE related to the use of combination therapy, there is, therefore, a strong argument to initiate therapy with multiple drugs (double or even triple therapy) immediately during hospitalisation or during the first visit, in the highest-risk patients – an approach that is already commonly used in the management of hypertension. Only with such an approach might we increase the number of patients on LDL-C goal, reduce the risk of discontinuation and side effects, and, consequently, reduce the risk of CVD events.

3 Overarching Aim

This position paper updates the 2021 ILEP recommendations and complements the existing guidelines on the management of lipid disorders in patients with ASCVD and after ACS. Bearing in mind the very high risk of further events in patients with ASCVD/ACS, we propose practical approaches to improve access and adherence to LLT in these patients. We also adopt the definition of an "extremely high-risk" group of individuals, which was introduced in 2021, and suggest strategies to urgently address the reduction of lipid-associated cardiovascular risk in these patients. The position paper is based entirely on evidence relating to the clinical effectiveness of LLTs, rather than pharmacoeconomic evaluations.

4 Development of Position Paper

The 2021 version of these recommendations was developed as part of the ACS EuroPath Central and South European Countries Project, and the methods have been described previously [24]. These updated guidelines were produced entirely as an initiative of the ILEP (https://ilep.eu).

In May 2023, the Steering Committee met online to discuss the progress of an update. Representatives from Bosnia and Herzegovina, Croatia, Czech Republic, Greece, Bulgaria, Hungary, Poland, Romania, Slovakia, Slovenia, and the United Kingdom (UK) were present. The experts from other countries were invited in the meantime. The content of the paper was also presented and widely discussed during the official ILEP meeting during the ESC meeting in Amsterdam (August 2023).

The experts discussed extensively the latest developments in evidence from clinical trials and real-world registries, as well as recent clinical guidelines and position papers relevant to the topic. The committee members shared details of current clinical practice, including the availability of lipid-lowering drugs, data gathering, organisation of healthcare systems, and strategies for optimal lipid management. They also identified ASCVD and especially post-ACS patients who are most in need of LLT intensification to understand the unmet needs. Based on this evidence, they discussed modifications to the recommendations.

During the draft stages, members of the WC had further online meetings. In March 2024, representatives from all countries updated the specific details of lipid-lowering practice in their countries, with a particular focus on areas for improvement. This information was included in the paper. Members of the Steering Committee summarised the information and presented draft practice recommendations that could be universally applicable in all states. These recommendations were circulated to all Steering Committee members and discussed using online fora until consensus was reached. They were released for the first time during the 2nd ILEP symposium in Lodz, Poland (22 April 2024), where the final version of the recommendations was discussed and approved.

The recommendations of the position paper are based on four principles, which emerged from the discussions of the WC:

- *Lower is better for longer:* The risk of cardiovascular events is effectively reduced by limiting exposure to LDL-C as early and as intensively as possible, including the upfront use of combination LLT.
- *Hard outcomes and real-world outcomes are the best:* Recommendations favour agents that have long-term follow-up in outcomes trials and registries (for effectiveness and safety).
- *Allow for personal and regional differences:* Recommendations are flexible in recognition of regional differences in availability and reimbursement for specific agents, healthcare systems specificity, national scientific recommendations, and patient factors relating to the choice to promote adherence with therapy.
- *Practical, not academic approach:* Recommendations put strong emphasis on the possibility of their introduction in clinical practice.

5 Current Situation in Europe

Information relating to the current status of LLT available for very high-risk patients, procedures for intensification of therapy, lipid measurement, follow-up, and rehabilitation

was collected for all countries participating in the development of the position paper (Table 1) and is summarised below.

5.1 Availability of Drugs and Reimbursement

In most countries represented, statins are widely available, usually with very little or no requirement for co-payment. However, there are still countries in which prescribing even with co-payment is only possible for specific clinical indications—sometimes based on not up-to-date evidence-based medicine, and lipid-lowering drugs might be prescribed only by specialists. Access to ezetimibe is restricted in some countries (for example, statin intolerance must be demonstrated), and in a few countries, prescription of ezetimibe is still limited only to selected specialists (cardiologists, endocrinologists). Similar situations exist in reference to FDC of statins and ezetimibe, and in some of the countries, FDC can be only administered after failure with monotherapy of statin and ezetimibe. Some limitations of FDC use might also be associated with the lack of full reimbursement of all preparations, especially with high statin doses. Availability of pitavastatin and bempedoic acid/FDC of bempedoic acid and ezetimibe differs largely between countries. Since the publication of the 2021 position paper, access to monoclonal antibody PCSK9Is has improved, but reimbursement and access to inclisiran is variable. In the UK, a commercial agreement has existed since 2021 between the manufacturer of inclisiran and the National Health Service (NHS), and inclisiran is recommended as an option in treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in patients with a history of cardiovascular events when LDL-C is > 100 mg/dL (2.6 mmol/L) despite maximally tolerated statin therapy (or in combination with other LLTs when statins are not tolerated or are contraindicated) [79]. In Poland, PCSK9Is and inclisiran are available within drug programme B101 for FH patients with LDL-C > 100 mg/dL (2.6 mmol/L) despite optimal LLT with statins and ezetimibe, and post-ACS patients (within 24 months) with additional risk factors (another MI or multivessel coronary artery disease [MVD] or peripheral artery disease [PAD] or stroke) and LDL-C > 70 mg/dL (1.8 mmol/L) despite optimal therapy of statins and ezetimibe for 3 months. In other countries there are differences in availability of PCSK9Is and inclisiran, mainly due to the lack of the CVD outcomes data for inclisiran (Table 1) [80].

Many guidelines and policies require ezetimibe to be used as a precondition for prescribing PCSK9I therapy. In this situation, the lack of access to ezetimibe effectively precludes PCSK9 therapy.

5.2 Intensification of Drug Therapy

Intensification of LLT at the ASCVD diagnosis and especially during hospitalisation and following discharge is a common problem, particularly when primary care is responsible for this task. As a result, rates of achieving LDL-C target values are low, and the recent data clearly showed that only 18–20% of patients achieved an LDL-C level of <55 mg/dL (<1.4 mmol/L) [17, 33, 34, 36]. The recent data also clearly showed that in most cases only combination therapy with statins, ezetimibe, and PCSK9 modulators (with and without bempedoic acid) allowed target achievement in patients at very high and extremely high cardiovascular risk [27, 81, 82]. A variety of reasons were provided for the failure to intensify statin therapy—many of which fell under the heading of "therapeutic inertia". Some countries reported a very hostile anti-statin movement in public media, a problem that has been observed elsewhere [83]. Unusual and non-evidence-based practices by general practitioners (GPs) and other medical specialists (such as regularly reducing the statin doses or recommending an annual "statin holiday") were also reported. Statins are strongly susceptible to the drucebo effect, whereby the expectation of adverse effects (particularly muscle pain), rather than the pharmacological effect of the drug, causes the patients to experience adverse effects [26, 84]. In light of this, some primary care physicians (but also cardiologists and other specialists) prescribe lower doses of statin than indicated because they believe that this will reduce the adverse effects and they fear that any adverse effect will lead to treatment cessation. In situations of polypharmacy, it was reported that patients and doctors often prioritised the use of other medicines for CVD over statins. There is also a phenomenon called "deprescription" of statins, especially observed in geriatrics patients. Another issue, that needs to be at least briefly mentioned is statin loading before, during, or after vascular interventions. One should remember that high-dose statin pretreatment is recommended for PCI and CABG according to current guidelines, and statin discontinuation should be avoided during acute cardiovascular events and vascular interventions [85]. Figure 1 presents the summary of the different activities that might effectively improve statin adherence and avoid discontinuation [16].

5.3 Follow-Up and Cardiac Rehabilitation

Common problems were identified with respect to availability and patients' engagement in cardiac rehabilitation programmes. In Poland, the Managed Care for Acute Myocardial Infarction Survivors (MACAMIS) [86, 87] has provided encouraging results. It has been optimised in the context of the targeted LDL-C (< 55 mg/dL/< 1.4 mmol/L)

Table 1 Summary of current approaches to LLT and challenges in participating countries

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Bosnia and Herzegovina (Federation B&H)													
No	No	GPs and specialists	Yes (40–60% for high-intensity statins). No co-payment for simvastatin	No	GPs and specialist	Yes (full price paid by a patient; no reimbursement)	No	No (even for "extremely high" risk patients)	No (only in one Canton reimbursed for small number of patients post ACS with LDL-C > 1.8 mmol/L despite optimal LLT with statins and EZE	No	No	Ensuring early and adequate use of new LDL-C-lowering drugs which should be reimbursed	LDL goal in discharge letter. Reimbursement of new LLT through special programmes for high-, very high-, and extremely high-risk patients
Bosnia and Herzegovina (Republic Srpska)													
No	No	Specialist	Yes (50%)	Yes	Specialist	Yes (no reimbursement)	Yes	Initiation restricted to cardiologists (HeFH without ASCVD, LDL-C > 5 mmol/L and maximally tolerated (max) statin + EZE; HeFH with ASCVD, LDL-C > 2.6 mmol/L and max statin + EZE; MI within 12 months LDL-C > 2.0 mmol/L and max statin + EZE). No co-payment	Initiation restricted to cardiologists (HeFH without ASCVD, LDL-C > 5 mmol/L and max statin + EZE; HeFH with ASCVD, LDL-C > 2.6 mmol/L and max statin + EZE; MI within 12 months LDL-C > 2.0 mmol/L and max statin + EZE). No co-payment	No	No	Ensuring adequate use of LDL-C-lowering drugs	Ensuring LDL goal is communicated in discharge letter. Education for GPs and patients regarding targets

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/ critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Bulgaria													
No	Yes	GPs and specialists	Yes	Yes	GPs and specialists	Yes	Yes	Reimbursement restricted to specialist centres. FH patients (DCLN ≥ 6): Very high-risk patients with LDL > 2.3 mmol/L after 2 months with max statin plus EZE; or extreme risk patients LDL > 1.6 mmol/L after 2 months with max statin plus EZE; or primary prevention > 3 mmol/L after 2 months with max statin plus EZE). Patients with ASCVD: Patients with MI or CABG and multivessel CAD if LDL > 2.3 mmol/L after 2 months with max statin and EZE; or in case of additional MI or multivessel disease or polyvascular disease if LDL 1.6 mmol/L after 2 months with max statin and EZE PCSK. Reimbursed at 75%	Reimbursement restricted to specialist centres. FH patients (DCLN ≥ 6): Very high-risk patients with LDL > 2.3 mmol/L after 2 months with max statin plus EZE; or extreme risk patients LDL > 1.6 mmol/L after 2 months with max statin plus EZE; or primary prevention > 3 mmol/L after 2 months with max statin plus EZE. Reimbursed at 75%	No	Reimbursed at 25% in patients with CAD	Lack of reimbursement of statin for primary prevention. Adoption of discharge little in secondary prevention. Increase proportion of patients referred to comprehensive care programme	Continuous education at all levels – GPs, cardiologists, and especially patients considering target levels

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/ critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Croatia													
Yes	Yes	GPs and specialists	No	Yes	Specialists	No	Yes (only in secondary prevention if LDL is higher than 2.6 mmol/L despite the maximum tolerated dose of statin)	Initiation restricted to specialists. ACS (with max statin + EZE); HeFH (LDL-C > 2.6 mmol/L with max statin plus EZE). No co-payment	Initiation restricted to specialists. ACS (with max statin + EZE); HeFH (LDL-C > 2.6 mmol/L with max statin plus EZE). No co-payment	No	No	Consistent achievement of LDL-C target	Education, particularly for GPs and patients regarding LDL-C targets and counter misinformation about LLT
Czech Republic													
Yes	Yes	GPs and specialists	No	No	GPs and specialists	No	No	Reimbursement restricted to specialist centres (LDL-C > 2.5 mmol/L with max statin plus EZE)	Reimbursement restricted to LDL-C > 2.0 mmol/L with max statin plus EZE	Reimbursement restricted	No	Follow-up referrals for optimal lipid management	Continuous education at all levels
Estonia													
Yes	Yes	GPs and specialists	No	No	GPs and specialists	No	No	Initiation restricted to cardiologists in post-ACS and FH patients (LDL-C > 3.0 mmol/L with max statin plus EZE)	Initiation restricted to cardiologists in post-ACS and FH patients (LDL-C > 3.0 mmol/L with max statin plus EZE)	No	No	Follow-up referrals for optimal lipid management	Education for GPs and patients regarding targets

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Germany													
No	No	GPs and specialists	No, only for pitavastatin	No	GPs and specialists	No	No	Initiation restricted to specialists. For patients not achieving LDL-C goals under maximal oral treatment in secondary prevention with an extra major risk factor and in patients with HeFH with severe family history or with Ho FH	Initiation restricted to specialists. For patients not achieving LDL-C goals under maximal oral treatment in secondary prevention and with an extra major risk factor and in patients with HeFH with severe family history or with Ho FH	Yes	Yes	Attainment of LDL-C targets	LDL goals should be clearly communicated in the hospital discharge letters. Education of both GPs and patients regarding LDL-C targets

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Greece													
No	Yes	GPs and specialists	Yes (small)	No	GPs and specialists	Yes (small)	No	Initiation restricted to specialists. In ASCVD when LDL > 100 mg/dL despite maximally tolerated statin + EZE, in progressive ASCVD within 2 years or in ASCVD + FH or ASCVD in young ones (< 50 years in men, < 55 years in women) when LDL > 70 mg/dL despite maximally tolerated statin + EZE, in primary prevention in FH (when LDL targets unmet). As well as in adults with mixed dyslipidaemia without ASCVD when LDL > 100 mg/dL despite maximally tolerated statin + EZE. No co-payment	Initiation restricted to specialists. In ASCVD when LDL > 100 mg/dL despite maximally tolerated statin + EZE, in progressive ASCVD within 2 years or in ASCVD + FH or ASCVD in young ones (< 50 years in men, < 55 years in women) when LDL > 70 mg/dL despite maximally tolerated statin + EZE, in primary prevention in FH (when LDL targets unmet). As well as in adults with mixed dyslipidaemia without ASCVD when LDL > 100 mg/dL despite maximally tolerated statin EZE. No co-payment	No	Yes	Need for consistent approach	Dissemination of national consensus paper

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Hungary													
Yes	Yes	GPs and specialists	Yes (max €3/month)	No	Specialists	Yes (max €2/Yes month)		Initiation restricted to specialists (internists and cardiologists). Secondary prevention (with max statin and EZE and unmet LDL-C target) and primary prevention in FH. Co-payment: (€1/month)	Initiation restricted to specialists (internists and cardiologists). Secondary prevention (with max statin and EZE and unmet LDL-C target). Co-payment: (€1/month)	No	No	Ensuring LDL-C is measured for all patients during index hospitalisation. Structured follow-up of patients by cardiologist and GPs	Ensuring LDL goal is communicated in discharge letter. Improve patient knowledge regarding importance of LDL-C reduction

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/ critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Italy													
No	Yes	GPs and specialists	No	Yes	GPs and specialists	No	Yes	Reimbursement restricted to specialist centres. FH patients (genetic diagnosis or DCLN ≥ 8). Very high-risk patients with ASCVD or T2DM with TOD and LDL > 1.8 mmol/L with max statin plus EZE)	Reimbursement restricted to specialist centres. FH patients (genetic diagnosis or DCLN ≥ 8). Very high-risk patients with ASCVD or T2DM with TOD and LDL > 1.8 mmol/L with max statin plus EZE)	Reimbursement restricted to patients requiring and LDL-C reduction less than 20% to reach their LDL-C target with max statin and/or EZE	No	Lack of reimbursement of statin MoAb PCSK9I and inclisiran in high-risk non-FH patients not complicated by severe ASCVD. Diabetics and mixed hyperlipidaemia patients often excluded because LDL-C calculated with the Friedewald formula. Bempedoic acid reimbursed based on the 2011 ESC-EAS guidelines LDL-C targets	Continuous education at all levels – GPs, cardiologists and patients considering target levels

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/ critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Israel													
Yes	Yes	GPs and specialists	No	No	GPs and specialists	No	No	Reimbursement and initiation restricted to specialists and cardiologists (LDL-C > 2.5 mmol/L with max statin plus EZE)	Reimbursement and initiation restricted to specialists and cardiologists (LDL-C > 2.5 mmol/L with max statin plus EZE)	No	No	Reduction of thresholds to levels in ESC guidelines	Education of patients and GPs
Kosovo													
Yes	No	Specialists	No	Yes	Specialists	No	No	Initiation restricted to specialists (clinical centre). HeFH (with max statin + EZE and LDL-C not at target), patients with very high risk. Fully reimbursed	Yes	No	No	Consistently reaching the LDL-C target	Education of health professionals and patients about the importance of the role of reducing LDL-C

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/ critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Latvia													
Yes (but not at the whole national level)	Yes	GPs and specialists	Yes (25%, co-payment if no revascularisation). No (if revascularised)	No	GPs and specialists	Yes (25%, co-payment if no revascularisation). No (if revascularised)	In combination with a statin, if LDL-C goal is not achieved with a non-high-intensity statin	Yes (100% in revascularised patients and 50% in non-revascularised HeFH patients; only with LDL-C > 3.0 mmol/L if on maximal tolerated statin plus EZE, or in case of their intolerance). Prescribed by a cardiologist, initiated *ex concilio*. LDL-C reduction by at least 40% required at 12 weeks to continue	Yes (100% in revascularised patients and 50% in non-revascularised HeFH patients; only with LDL-C > 3.0 mmol/L if on maximal tolerated statin plus EZE, or in case of their intolerance). Prescribed by a cardiologist, initiated *ex concilio*. LDL-C reduction by at least 40% required at 12 weeks to continue	No	No	It should be allowed to start with statin + EZE combination upfront. Reimbursement of MoAbs and inclisiran should be extended to non-revascularised patients and lower LDL-C levels. Reimbursement of MoAbs and inclisiran should be 100% in HeFH patients and also for primary prevention. Bempedoic acid should become available	Continuous education is important, but also systemic monitoring of actual LDL-C levels should be introduced

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Lithuania													
Yes	Yes	GPs and specialists	No	No	GPs and specialists	No	No	Available (only out of pocket). No reimbursement at all for any condition	Available (only out of pocket). No reimbursement for any condition	Registered in Lithuania, but not available yet	No	Reimbursement of MoAb PCSK9I and inclisiran is urgently needed. Availability of bempedoic acid, registration, and availability of pitavastatin would be an advantage. Consistent achievement of LDL-C target with drug combinations	Continuous education at all levels. Patient education to counter misinformation and improve adherence, compliance, and persistence. Fighting with fake news and myths on social media. More patients at LDL-C goal. National survey for LLT

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/ critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Poland													
Yes	Yes	GPs and specialists	Yes (small)	No	GPs and specialists	Yes (small)	No (some FDC preparations of statins and EZE for the highest statin doses are not fully reimbursed)	Initiation restricted to cardiologists. Confirmed FH (+ LDL-C > 100 mg/dL despite 3-month optimal statin + EZE therapy). Very high/ extreme risk after AMI (within 24 months + LDL-C > 70 mg/dL despite 3-month optimal statin + EZE therapy + additional conditions like another MI or PAD/stroke/ TIA or MVD)	Initiation restricted to cardiologists: confirmed FH (+ LDL-C > 100 mg/dL despite 3-month optimal statin + EZE therapy) Very high/ extreme risk after AMI (within 24 months + LDL-C > 70 mg/dL despite 3-month optimal statin + EZE therapy + additional conditions like another MI or PAD/stroke/ TIA or MVD)	Not available (few patients have been treated within target import)	Yes	Increase the number of patients treated with suitable doses of statins and especially with upfront lipid-lowering combination therapy. Fighting against nocebo/ drucebo effect and the large proportion of patients with statin intolerance. Increase proportion of patients referred to comprehensive care programme and to drug programme B101 for PCSK9 targeted therapy (which should be less restrictive)	National and local well-designed education campaigns for physicians and patients. Fighting with fake news on statins and LDL-C. Increase awareness on lipid disorders as a CVD risk factor

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Romania													
Yes	Yes	GPs and specialists	Yes (10%)	No	GPs and specialists	Yes (50%)	No	Initiation restricted to specialists. Eligibility (ACS, high-risk patients, FH, statin intolerance) based upon current LLT and unmet LDL-C targets. Fully reimbursed	Initiation restricted to specialists. Eligibility (selected high-risk patients, FH, statin intolerance) based upon current LLT and unmet LDL-C targets. Fully reimbursed	No	No	Ensuring LDL-C is measured for all individuals at risk of CV disease. Consistent achievement of LDL-C target	Increasing use of SCORE2 & OP to measure the cardiovascular risk. Improve patient knowledge regarding importance of LDL-C reduction

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/ critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Slovakia													
Yes	Yes	GPs and specialists	Yes (small)	No	GPs and specialists	No	No	Initiation restricted to specialists. Treatment must be approved in advance by insurance company. Restricted to defined patient population with very high LDL-C threshold. Fully reimbursed	Initiation restricted to specialists. Treatment must be approved in advance by insurance company. Restricted to defined patient population with LDL-C threshold of 2.6 mmol/L (100 mg/dL). Fully reimbursed	Initiation restricted only as second-line therapy in case of muscular adverse events on first-line statin therapy. No possibility to add on to statin up to date. Approval in advance not necessary. Available as monotherapy and FDC with EZE. Small co-payment	No	Therapeutic inertia	Patient education to counter misinformation and improve adherence

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
Slovenia													
No (local registries exist)	Yes	GPs and specialists	No	No	GPs and specialists	No	Yes (for monotherapy in statin intolerance and low/moderate CV risk)	Initiation restricted to specialists. Full reimbursement, no co-payment with the following restrictions: secondary prevention with LDL-C > 2.6 mmol/L with max tolerated statins + EZE; or primary prevention: (HeFH) and LDLC > 3.6 mmol/L with maximally tolerated statins + EZE; or statin intolerance (2 statins) – same restrictions regarding the LDL-C as above on EZE monotherapy. All included patients are followed in PCSK9 registry	Restrictions and reimbursement rules are the same as for the PCSK9I MoAb	No	No	Mandatory input into ACS registry	Educational needs for patients, national survey (for quality control)
Switzerland													
Yes	Yes	GPs and specialists	No	No	Specialists	No	Yes	Initiation restricted to specialists. Treatment must be approved in advance by insurance company. Restricted to defined patient population with very high LDL-C threshold. Fully reimbursed	No	No	No	Therapeutic inertia	Patient education to counter misinformation and improve adherence

Table 1 (continued)

ACS registry	ACS guidance	Statin availability			Ezetimibe availability			Availability of other agents				Unmet needs	Educational/ critical needs
		Initiation	Co-payment	Restrictions	Initiation	Co-payment	Restrictions	MoAb PCSK9I	Inclisiran	Bempedoic acid	Pitavastatin		
United Kingdom of Great Britain and Northern Ireland													
Yes	Yes	GPs and specialists	No	No	GP and specialists	No	No	If non-HDL-C remains > 2.5 mmol/L despite other LLTs	Recommended in FH or secondary prevention when LDL-C persistently > 2.6 mmol/L despite maximally tolerated statin therapy	Recommended in combination with EZE when statins are not tolerated	No	Increased proportion of patients reaching targets	Continuous education at all levels

Current approaches to LLT and challenges: 1. Availability of ACS registry. 2. Availability of special guidelines on how to manage ACS patients. 3. Statin availability (free to all, free but only in the special clinical scenarios, not available). 4. Ezetimibe availability (as above, with the clear information on who might prescribe this). 5. PCSK9Is restrictions and availability of other agents. 6. Unmet needs/gaps. 7. Educational needs/critical needs for improvement

ACS acute coronary syndrome, *AMI* acute myocardial infarction, *ASCVD* atherosclerotic cardiovascular disease, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CV* cardiovascular, *CVD* cardiovascular disease, *DLCN* Dutch Lipid Clinic Network, *EAS* European Atherosclerosis Society, *ESC* European Society of Cardiology, *EZE* ezetimibe, *FDC* fixed dose combination, *FH* familial hypercholesterolaemia, *GP* general practitioner, *HeFH* heterozygous familial hypercholesterolaemia, *HoFH* homozygous familial hypercholesterolaemia, *HDL-C* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein, *LDL-C* low-density lipoprotein cholesterol, *LLT* lipid-lowering therapy, *MI* myocardial infarction, *MoAb* monoclonal antibody, *MVD* multivessel coronary artery diseases, *PAD* peripheral artery disease, *PCSK* proprotein convertase subtilisin/kexin, *PCSK9* PCSK type 9, *PCSK9I* PCSK type 9 inhibitor, *T2DM* type 2 diabetes mellitus, *TIA* transient ischemic attack

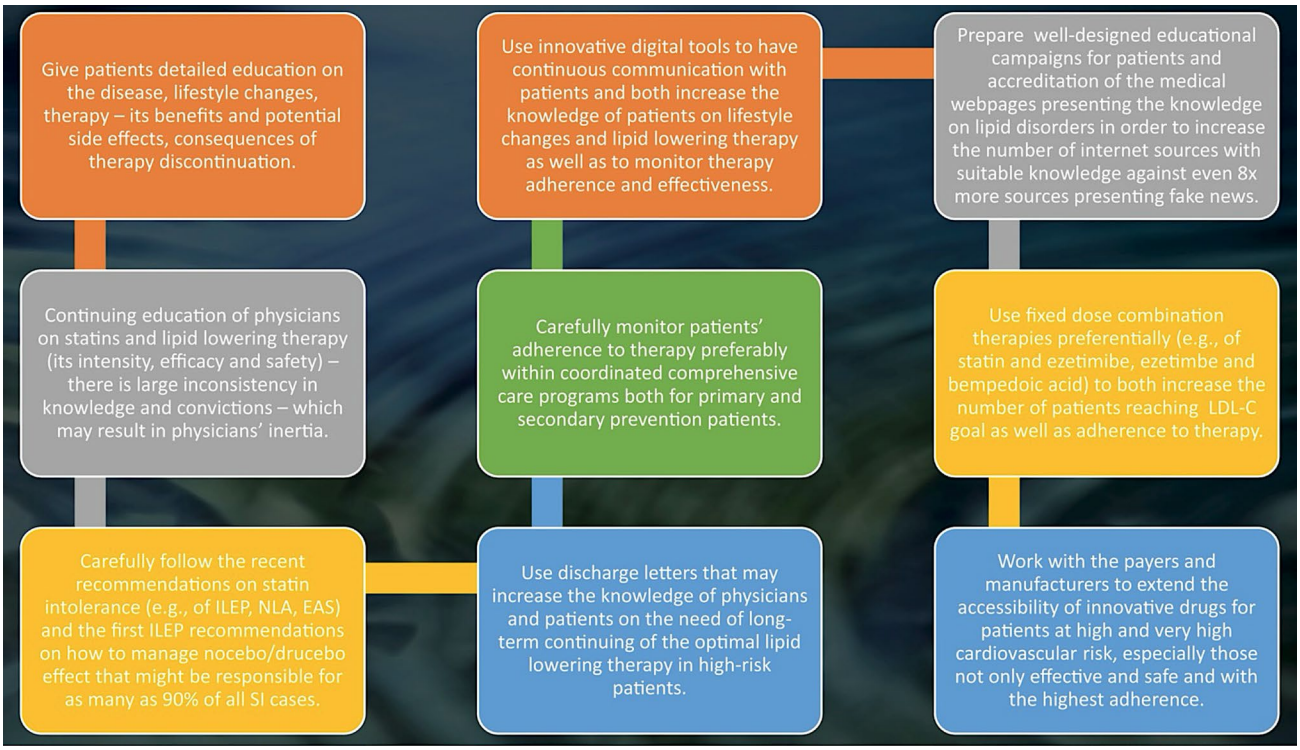

Fig. 1 The summary of the different activities that might effectively improve statin adherence and avoid discontinuation. Based on the Eur Heart J Open. 2022 Oct 26;2(6):oeac071 [16] with permission (licence number: 5820250572831). *EAS* European Atherosclerosis Society, *IlEP* International Lipid Expert Panel, *LDL-C* low-density lipoprotein cholesterol, *NLA* National Lipid Association, *SI* statin intolerance

and a success fee for patients being on the LDL-C goal after 12 months. Now, there is an ongoing discussion on its possible extension to 24 months; unfortunately, similar services are not universally available in all countries. There was significant variability in the extent to which interventional cardiologists were involved in follow-up coordinated care. This highlights the need for a standardised pathway for acute therapy and discharge and points out that objective quality control measures are required to evaluate rehabilitation services.

6 Recommendations

The recommendations for optimal LLT in ASCVD patients, including very high-risk/extremely high-risk individuals such as those with ACS, are presented below, as a main treatment pathway, with additional pathways for some specific clinical practice scenarios. The pathways are based upon the principles of LDL-C reduction: the earlier the better, the lower the better, the longer the better [77, 78]. The pathways are also firmly based on the EAS/ESC guidelines for the management of dyslipidaemias [22], albeit with a greater emphasis on reducing delays in starting lipid-lowering, particularly in those individuals at the greatest risk of first and recurrent events.

It is important that both patients and prescribers are reassured about the safety of achieving very low levels of LDL-C as demonstrated repeatedly in clinical trials and registries [43–45, 69–72].

The main pathway for optimal LLT post ACS can be divided into three sections (Figs. 2, 3, 4, 5):

- Diagnosis and stratification
- Target-driven LLT
- Support and follow-up

In the diagnosis and stratification stage, some patient groups are identified for special pathways. These include patients with FH or extremely high ASCVD risk (Sect. 6.2.1; Fig. 3), statin intolerance (Sect. 6.2.2; Fig. 4), and ASCVD with metabolic disorders (pre-diabetes/metabolic syndrome/diabetes) (Sect. 6.2.3; Fig. 5). In the previous version of the recommendations (April 2021) [24], as we then were introducing the upfront lipid-lowering combination therapy for the first time, we put a lot of attention into the baseline level of LDL-C in very high-risk

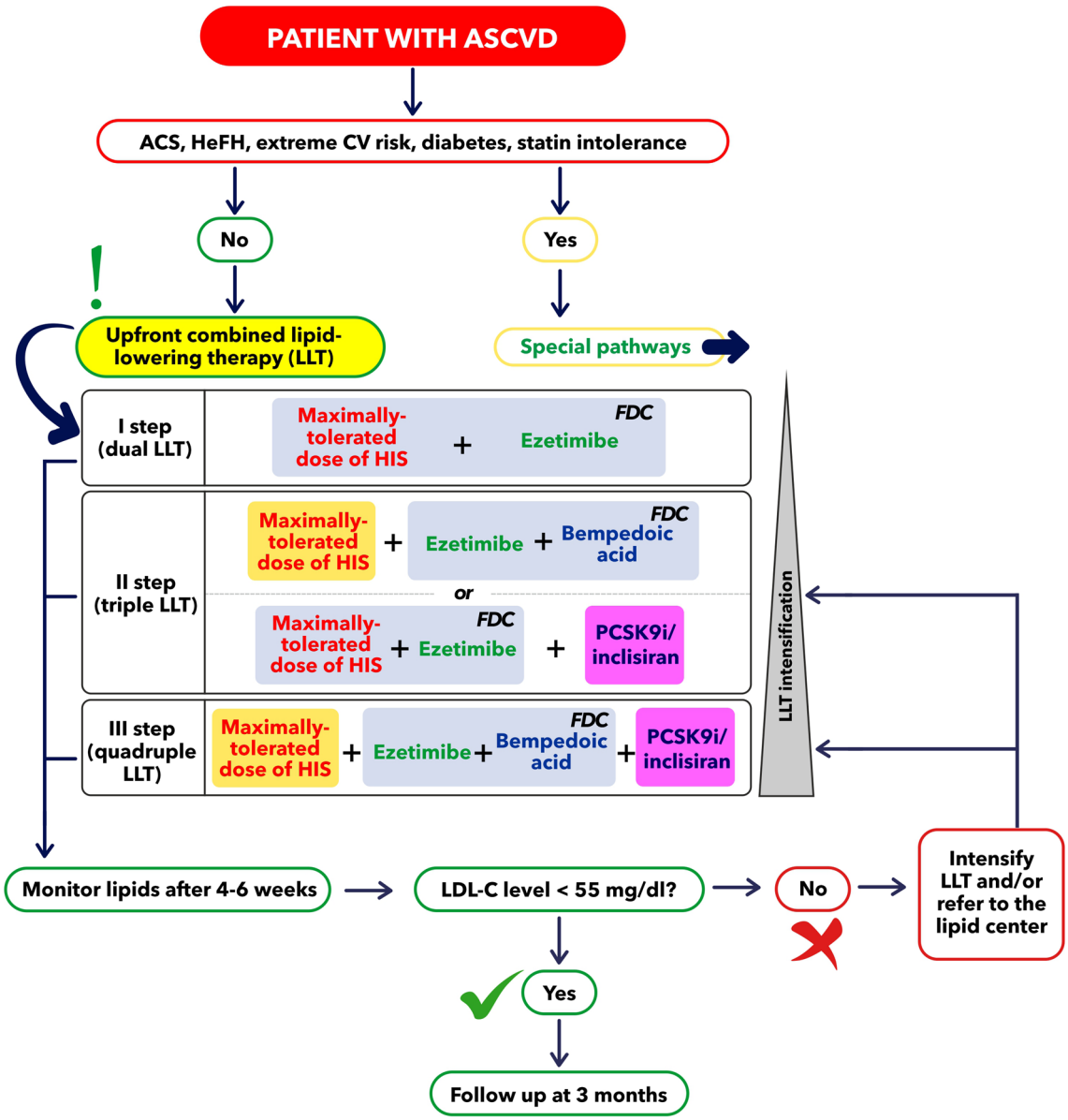

Fig. 2 Overall pathway of optimal LLT in ASCVD patients. The pathway is divided into three stages: (1) diagnosis and stratification; (2) target-driven lipid-lowering therapy; (3) support and follow-up. Special pathways are provided for specific treatment groups, including those with extreme CV risk (as defined in this document), familial hypercholesterolaemia, statin intolerance, and diabetes/metabolic disorders. At each step of LLT, adherence should be carefully monitored. *ACS* acute coronary syndrome, *ASCVD* atherosclerotic cardiovascular disease, *CV* cardiovascular, *FDC* fixed dose combination, *HeFH* heterozygous familial hypercholesterolaemia, *HIS* high intensity statin, *LDL-C* low-density lipoprotein cholesterol, *LLT* lipid-lowering therapy, *PCSK9I* proprotein convertase subtilisin/kexin type 9 inhibitor

patients. Based on the data we have obtained since that time (Sect. 1.3.3.), as well as other recommendations recently published [20, 25], we strongly believe that this is no longer important (especially following the rules of the lower the better for longer, and the earlier the better), and the previous approach may result in treatment initiation with intensive statin therapy alone, when the patient would benefit from combination therapy. Obviously, monitoring of LDL-C at baseline and after therapy introduction is critically important, but it should not decide on the introduction of the initial upfront lipid-lowering combination therapy, which in the end, increases the number of patients on LDL-C goal, reduces the number of side effects and discontinuations (improves adherence), and reduces the CVD burden in this population.

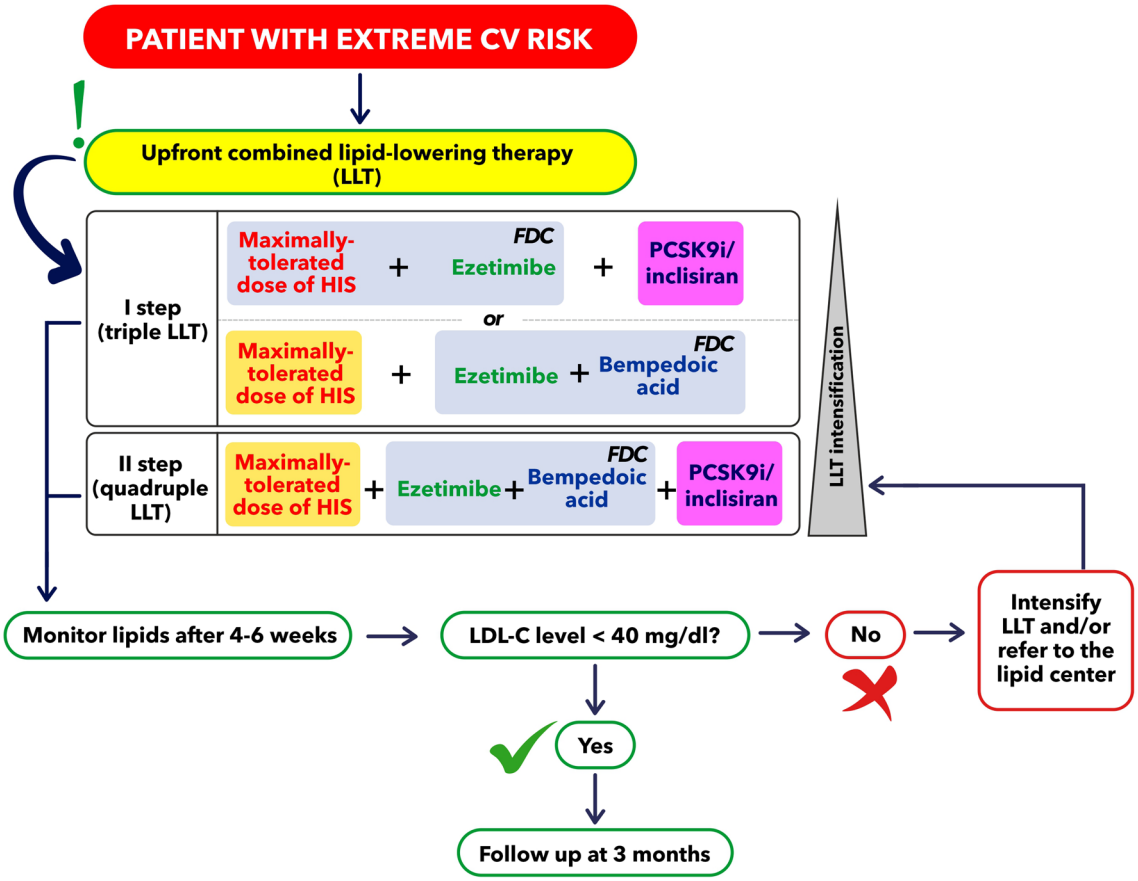

Fig. 3 Special pathway for patients with extreme CV risk. At each step of LLT, adherence should be carefully monitored. *CV* cardiovascular, *FDC* fixed dose combination, *HIS* high-intensity statin, *LDL-C* low-density lipoprotein cholesterol, *LLT* lipid-lowering therapy, *PCSK9I* proprotein convertase subtilisin/kexin type 9 inhibitor

6.1 General Considerations

Notwithstanding the fact that the recommendations in this position paper are made in the context of the best-available outcomes-driven evidence and expert opinion, it is recognised that a personalised approach to therapy is often optimal to promote adherence in the context of patient-centred care. The issues of personalisation and adherence and their impact on treatment pathways are addressed below.

6.1.1 Adherence

According to the concept of "lower is better for longer", the best outcomes for patients will be achieved when lipid-lowering is sustained over a long period of time. It is critically important to underline that in the case where low or even very low LDL-C levels are obtained with LLT, it is not recommended to deescalate the treatment (if well-tolerated) with, e.g. statin dose reduction or ezetimibe withdrawal or PCSK9 targeted therapy discontinuation. It is recommended to keep this therapy, as it ensures further reduction of the risk of CVD outcomes and mortality without any safety concern. The lower-the-better-for-longer approach requires adherence to therapy, which can be challenging. It has been demonstrated that the median time to discontinuation after the initiation of statin therapy is 15 months [16], and the recent SANTORINI study found that 22% of adults at high- or very high-risk of CVD were receiving no LLT at all [17]. Not less important than this alarming situation is the propensity of prescribers and patients to reduce (or fail to escalate) the dose of statins when ezetimibe (or other add-on therapies) is prescribed. This can be considered another form of suboptimal adherence whereby patients do not receive the maximal intensity of LLT they can tolerate. The reasons for this are multifactorial and include therapeutic inertia, in addition to concern about adverse effects. In the context of statin therapy, the ILEP has produced a position paper outlining how adherence can be improved through education and careful identification of genuine statin intolerance (see the MEDS [Minimize, Educate, Diet/nutraceuticals, Symptoms/

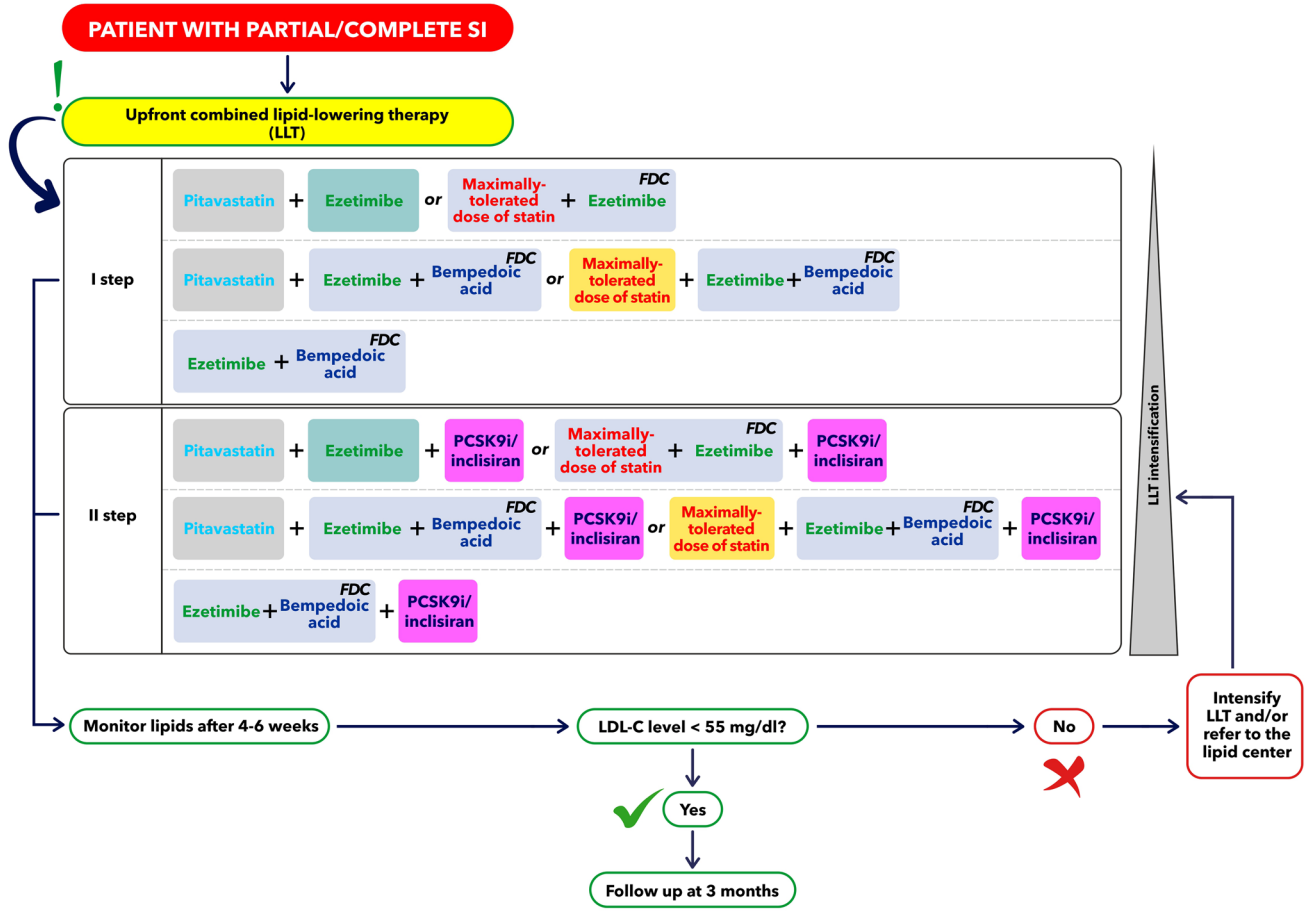

Fig. 4 Special pathway for participants with objectively confirmed partial/complete statin intolerance. At each step of LLT, adherence should be carefully monitored. *FDC* fixed dose combination, *LDL-C* low-density lipoprotein cholesterol, *LLT* lipid-lowering therapy, *PCSK9I* proprotein convertase subtilisin/kexin type 9 inhibitor

biomarkers] algorithm in the paper) [26]. The most common reasons for non-adherence are presented in Figure 6 [44].

6.1.2 Personalisation

Person-centred care and personalisation of therapy can be used to enhance patient engagement with the treatment process and, thereby, improve adherence. This may mean taking decisions that are supported by less robust evidence than the recommendations make, but which are nevertheless rational and justifiable.

Such an approach may be used to overcome clinically documented adverse effects of statin therapy. In patients who can tolerate a moderate dose of statin (but not high-intensity therapy), data from the RACING trial suggest that substantial benefit can be achieved by combining a lower dose with ezetimibe, which is also the truth in the difficult-to-treat populations, such as those with diabetes and at older age [37–39]. This should not be used as a reason to not escalate statin therapy, whenever it can be made, but may be an option for relevant patients. In fact, these data and others bring us closer to the recommendation that in patients at risk of diabetes (those with obesity, pre-diabetes, metabolic syndrome) and those with a history of statin intolerance and/or statin-intolerance risk factors, we might consider starting with the upfront lipid-lowering combination therapy of moderate-intensity statin therapy (or preferably with the lower dose of high intensity statin [HIS], e.g. rosuvastatin 20 mg, to avoid excuses for not using high doses of statins) with ezetimibe plus other non-statin drugs (depending on risk and required LDL-C reduction; the agents without such a risk are, e.g. bempedoic acid or PCSK9 modulators). While it is still not in the official guidelines, more and more evidence suggests such a personalised approach [8, 28, 38, 39, 73].

Similarly, personalisation may be considered when patients struggle to comply with dosing regimens. Daily dosing of "small-molecule" drugs such as statins and ezetimibe will always present a challenge to adherence in some patients. However, even the frequency of injections required for monoclonal antibody PCSK9Is may be difficult for busy

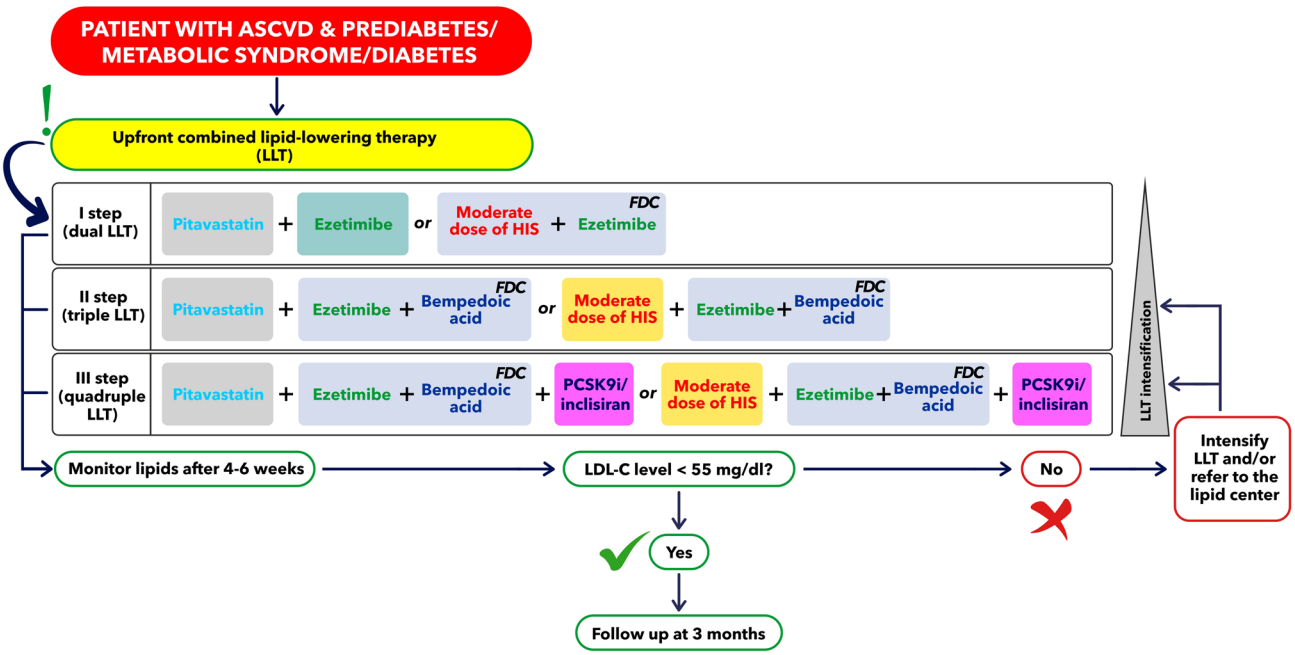

Fig. 5 Special pathway for participants with ASCVD and metabolic disorders. At each step of LLT, adherence should be carefully monitored. *ASCVD* atherosclerotic cardiovascular disease, *FDC* fixed dose combination, *HIS* high-intensity statin, *LDL-C* low-density lipoprotein cholesterol, *LLT* lipid-lowering therapy, *PCSK9I* proprotein convertase subtilisin/kexin type 9 inhibitor

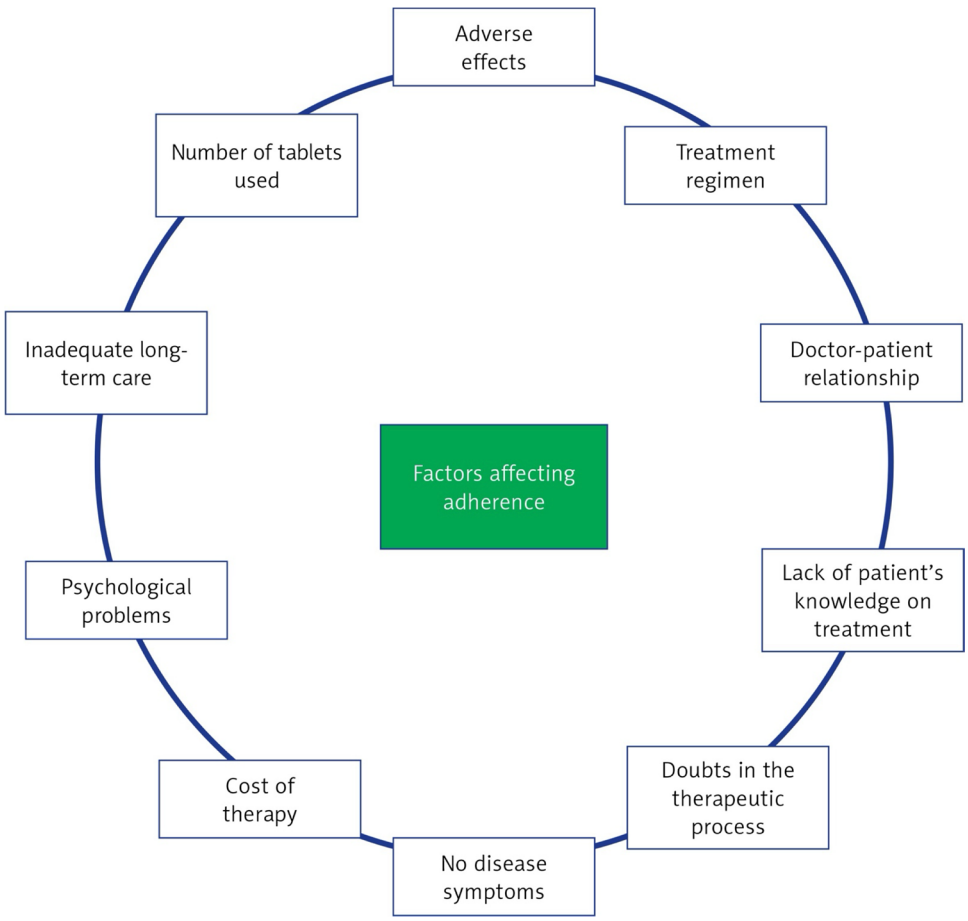

Fig. 6 Key reasons for non-adherence based on the PoLA Lipid Guidelines 2021 [44] with permission. *PoLA* Polish Lipid Association

individuals. In this context, inclisiran, despite its less extensive evidence base, may present an attractive option.

6.2 Special Pathways

The diagnosis and stratification stage identifies groups of patients who need care that differs from the standard pathway. Advice relating to these groups is provided below.

6.2.1 Extreme Cardiovascular Risk

The current ESC/EAS dyslipidaemia guidelines (2019) include all ACS patients in a "very high-risk" category. However, these guidelines [22] are incomplete concerning the definition of extremely high-risk patients (patients after MI and other vascular event in last 2 years) [11–13, 88–90]. The definition of "extremely high risk" proposed in the 2021 ILEP position paper [24] has been retained here, with minor modifications based on the most recent data and published guidelines [90].

Patients fulfilling any of the following criteria (not being on the LDL-C target despite intensive/maximally tolerated statin therapy and ezetimibe) should be considered to be at extremely high-risk:

- MI + previous vascular event in the last 2 years
- ACS + MVD
- ACS + PAD or PVD
- ACS + FH
- ACS + diabetes mellitus + at least one additional risk factor (hsCRP > 2 mg/L and/or chronic kidney disease [21] and/or Lp(a) > 50 mg/dL [125 nmol/L]).

The extremely high-risk nature of this group demands a lower target for LDL-C (< 40 mg/dL [1 mmol/L]). In order to minimise delay in achieving this lipid target in these individuals and bearing in mind the potential difficulties in attaining the lower target, at least dual therapy should be considered initially and immediately, using maximally tolerated statin therapy and ezetimibe. However, preferably the triple therapy (if feasible to be implemented) should be considered [25] to have these patients as low as possible and as early as possible regarding LDL-C levels. When LDL-C target is not achieved (e.g. in patients with high baseline LDL-C levels, non-responders, statin-intolerant patients, and/or FH ones), quadruple LLT (if available) should be administered. In this case, FDC is highly recommended to reduce the number of drug interventions and to improve compliance (Fig. 3). Considering the limited data concerning the group of extremely high-risk patients (based on the subgroup analyses), the prospective validation of this group is still necessary.

6.2.2 Statin Intolerance

If complete statin intolerance has been confirmed using objective criteria (usually applying to < 3% of patients with statin therapy) [66, 67], the treatment should proceed immediately using non-statin LLT, including bempedoic acid/ezetimibe FDC therapy, where available (Fig. 4). In the case of partial statin intolerance, the main pathway (Fig. 4) allows for combination therapy with a maximally tolerated statin dose and additional LLTs. In this situation, consideration should be given to upfront initiation of additional LLTs in combination with a low to moderate dose of statin (ideally as FDC to improve adherence) rather than delaying target attainment by slow, gradual upward titration of the statin dose. Such an approach allows us to reduce the risk of LDL-C visit-to-visit variability, which is associated with a significant increase in recurrent CVD events [91].

6.2.3 Patients with ASCVD and Diabetes/Metabolic Disorders

In the 2024 ILEP recommendations, based on the numerous new data on LLT indicating it might be not only effective in the reduction of LDL-C but also might be neutral or even protective against NOD, we have decided to separately present the personalised approach for this group of patients. It seems to be critically important as we now face the epidemic of obesity and diabetes – the prevalence of overweight and obesity may be as high as 40% in the population, and diabetes will soon exceed 10% (and will double by 2050) in most of high-income countries [92, 93].

In very high-risk patients with ASCVD and diabetes or metabolic disorders (those with obesity, pre-diabetes, and/or metabolic syndrome) (excluding patients with diabetes meeting the definition of the extreme CVD risk), we should consider upfront lipid-lowering combination therapy of pitavastatin (with ezetimibe) (Sect. 1.3.4), which may reduce LDL-C by even 47% and is associated with a reduction of the NOD risk [29], or a lower dose of high-intensity statin (rosuvastatin 20 mg or atorvastatin 40 mg) and ezetimibe (as FDC) – to significantly reduce LDL-C, not increase the risk of NOD, and reduce other side effects and/or discontinuation (Fig. 5). If the target cannot be achieved, we should consider bempedoic acid (if available) (Sect. 1.3.4), which may also help to optimise both LDL-C therapy and FBG/HbA1c (based on the available data, bempedoic acid significantly increases the chance to achieve both LDL-C and HbA1c targets [48]) and/or PCSK9 modulators (if available) [94, 95].

Table 2 Proposal of wording of a discharge letter of a post-acute coronary syndrome patient. Modified based on the Polish discharge letter [80]

You are a patient who has had a myocardial infarction (heart attack). In order to reduce the risk of another heart attack, as well as to reduce the risk of stroke or atherosclerosis of the arteries of the lower extremities (manifested by pain in the calves or thighs when walking), which can lead to amputation of a limb, it is necessary to follow the recommendations established by the scientific societies. After a myocardial infarction, low-density lipoprotein cholesterol (LDL-C) should be regularly monitored, and target LDL-C values of < 55 mg/dL (< 1.4 mmol/L) should be achieved. This goal can be achieved by:
1. Taking the highest possible doses, as long as they are well tolerated, of potent statins (atorvastatin or rosuvastatin), or if baseline LDL-C levels are very high, start right away with a combination of a statin and ezetimibe
2. If after 4–6 weeks the LDL level is above 55 mg/dL (1.4 mmol/L), immediately add ezetimibe to atorvastatin or rosuvastatin
3. If after another 4–6 weeks the LDL-C is still not below 55 mg/dL (1.4 mmol/L), add proprotein convertase subtilisin/kexin type 9 protein inhibitor (alirocumab, evolocumab – subcutaneous injection every 2–4 weeks) or inclisiran (subcutaneous injection administered twice a year) to statin and ezetimibe. *Note:* Some patients can receive these drugs for free under a reimbursement programme funded by the Ministry of Health and the National Health Fund. Please always ask your family doctor or cardiologist at the clinic about the possibility of participating in this programme
4. In addition to lowering LDL-C < 55 mg/dL (< 1.4 mmol/L), you should change your lifestyle (healthy diet, regular physical activity of individually selected intensity) and control other atherosclerosis risk factors: effectively treat hypertension, diabetes, and obesity and do not smoke cigarettes or use other tobacco products

6.3 Support and Follow-Up

Particular consideration should be given to communication at the interface of secondary and primary care, with the aim of maximising adherence to the treatment pathway, follow-up, and escalation of LLT. A standardised discharge letter that is now applied commonly in Departments of Cardiology in Czechia, Poland, Romania, and France should be used for all patients [80, 96]. It is particularly important to include personal LDL-C goals and specific instructions about how and when treatment should be escalated if treatment targets are not achieved. Furthermore, the letter should describe the process of regular monitoring (including telemonitoring, e-visits, e-advice, e-prescriptions, e-referrals). An example of such a discharge letter and its content is presented in Table 2.

Acknowledgements The preparation of these updated recommendations was achieved through meetings of the Steering Committee, managed entirely by the International Lipid Expert Panel (ILEP). No pharmaceutical company had any role in the writing of this position paper.

Declarations

Funding No external funding was used in the preparation of this article.

Conflict of interest *Dr. Banach* has received research grant(s)/support from Amgen, Daiichi-Sankyo, Mylan/Viatris, and Sanofi, and has received honoraria and/or served as a consultant for Adamed, Amgen, Daiichi-Sankyo, Esperion, Kogen, KRKA, Lilly, MSD, Mylan/Viatris, NewAmsterdam Pharma, Novartis, Novo Nordisk, Polfarmex, Polpharma, Sanofi-Regeneron, Servier, Teva, and Zentiva. *Dr. Reiner* has received honoraria from Sanofi and Novartis. *Dr. Cicero* has received personal fees from Mylan-Viatris, Sharper, and Servier. *Dr. Dyrbuś* has received fee for scientific activities from Novartis, Sanofi-Aventis, and Amgen. *Dr. Fedacko* has received a consultancy fee from Sanofi, Amgen and Novo Nordisk, and a research grant from Pfizer. *Dr. Fras* has received grants and fees for scientific activities from Amgen, Krka, Novartis, Swix BioPharma, and Viatris. *Dr. Gaita* has received honoraria from Amgen, AstraZeneca, Bayer, Berlin Chemie, Biofarm, Boehringer Ingelheim, Galenica, GSK, Gedeon Richter, Krka, MSD, Novartis, Novo Nordisk, Pfizer, Sanofi, Servier, Terapia, Vifor Pharma, and Zentiva. *Dr. Gierlotka* reports honoraria from Sanofi, Novartis, Bayer, Amgen, Novo Nordisk, AstraZeneca, Servier. *Dr. Gouni-Berthold* has served as consultant and received honoraria from Akcea, Amgen, Daiichi-Sankyo, Novartis, Sanofi-Regeneron, Ultragenyx, and Amarin. *Dr. Jankowski* has received a research grant from Sanofi and has served as a consultant for Novartis, Servier, and Zentiva. *Dr. Járai* has served as a consultant for and received honoraria from Bayer, Berlin-Chemie, Boehringer Ingelheim, Egis, MSD, Novartis (Sandoz), Novo Nordisk, Pfizer, Richter Gedeon, Sanofi, Servier, and Teva. *Dr. Latkovskis* has given talks, attended conferences, received consultancy fees, and/or participated in trials sponsored by Abbott Laboratories, Amgen, AstraZeneca, Berlin-Chemie/Menarini, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Grindex, KRKA, MSD, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi, Servier Laboratories, Siemens Laboratories, and Zentiva. *Dr. Magda* has received consultation fees from Novartis, Sanofi, and Servier. *Dr. Margetic* has received a fee for scientific activities from Novartis and Sanofi. *Dr. Ostadal* has received honoraria from Getinge, Abiomed, Edwards, Fresenius/Xenios, AstraZeneca, Bayer, Boehringer Ingelheim, Amgen, Sanofi, Servier, Novartis, Pfizer, AOP, and GSK. *Dr Paragh* has received lectures fees from Hungarian branches of Novartis, Richter Gedeon, and Sandoz. *Dr. Paneni* has received honoraria from Novo Nordisk. *Dr. Pećin* has received grants and fees for scientific activities from Amgen, Bayer, Novartis, and Sanofi. *Dr. Pella* has received grant support and honoraria from Sanofi, Amgen, MSD, Servier, Novartis, and Pfizer. *Dr. Postadzhiyan* reports fees for educational activities from Amgen, AstraZeneca, KRKA, Novartis, Servier, Teva, and Zentiva. *Dr. Stoian* has given lectures, received honoraria and research support, and participated in conferences, advisory boards, and clinical trials sponsored by pharmaceutical companies, from AstraZeneca, Amgen, Boehringer Ingelheim, Coca-Cola, Eli Lilly, Merck, Medtronic, MSD, Medochemie, Novo Nordisk, Novartis, Roche Diagnostics, Servier, Sandoz, and Sanofi. *Dr. Trbusic* has received a fee for scientific activities from Novartis and Sanofi. *Dr. Udroiu* has received a fee for scientific activities from AstraZeneca and Pfizer. *Dr. Viigimaa* reports fees for educational activities from Amgen, AstraZeneca, Novartis, Novo Nordisk, Menarini, Servier, and Swixx BioPharma. *Dr. Vinereanu* has received research grants and expert fees from Amgen, Sanofi, Novartis, and Servier. *Dr. Vlachopoulos* has received grants and fees

for scientific activities from Amgen, Sanofi, and MSD. *Dr. Vrablik* has received personal fees from Abbott, Amgen, AstraZeneca, BMS, Genzyme, KRKA, MSD Idea, Novartis, Pfizer, and Sanofi-Regeneron. *Dr. Vulic* has received a fee for scientific activities from Sanofi. *Dr. Penson* owns four shares in AstraZeneca PLC and has received honoraria from Amgen and Sanofi and travel/accommodation reimbursement for events sponsored by AKCEA, Amgen, AMRYT, Link Medical, Mylan, and Napp. *All other authors* declare that they have no potential conflicts of interest that might be relevant to the contents of this article.

Authors' contributions *Dr. Banach:* Conceptualisation; data curation; methodology; project administration; supervision; validation; visualisation; writing, reviewing, and editing; revisions; preparing the final version of the paper. *Dr. Penson:* Data curation; investigation; methodology; validation; visualisation; first draft preparation; reviewing and editing. *Dr Surma:* data curation, visualisation, draft figures preparations; reviewing and editing. *Drs. Reiner, Bajraktari, Bielecka-Dabrowa, Bunc, Bytyçi, Ceska, Cicero, Dudek, Dyrbuś, Fedacko, Fras, Gaita, Gavish, Gierlotka, Gil, Gouni-Berthold, Jankowski, Járai, Jóźwiak, Katsiki, Latkovskis, Magda, Margetic, Margoczy, Mitchenko, Durak-Nalbantic, Ostadal, Paragh, Petrulioniene, Paneni, Pećin, Pella, Postadzhiyan, Stoian, Trbusic, Udroiu, Viigimaa, Vinereanu, Vlachopoulos, Vrablik*, and *Vulic*: Investigation, methodology; validation; writing, reviewing, and editing; final revisions and approval.

Data availability statement Data sharing is not applicable to this article as no datasets were generated for this article.

Ethics approval Not applicable.

Code availability Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

References

1. Roth GA, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol. 2020;76(25):2982–3021.
2. Mensah GA, et al. Global burden of cardiovascular diseases and risks, 1990–2022. J Am Coll Cardiol. 2023;82(25):2350–473.
3. Timmis A, et al. European Society of Cardiology: cardiovascular disease statistics 2019. Eur Heart J. 2020;41(1):12–85.
4. GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024; 403(10440):2100–2132.
5. Barbato E, et al. Mapping interventional cardiology in Europe: the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Atlas Project. Eur Heart J. 2020;41(27):2579–88.
6. Ference BA et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38(32):2459–2472.
7. Banach M, Surma S. A look to the past—what has had the biggest impact on lipids in the last four decades? A personal perspective. Arch Med Sci. 2023;19(3):559–64. https://doi.org/10.5114/aoms/166256.
8. Banach M, et al. Bempedoic acid in the management of lipid disorders and cardiovascular risk. 2023 position paper of the International Lipid Expert Panel (ILEP). Prog Cardiovasc Dis. 2023;79:2–11.
9. Ray KK, et al. Efficacy and safety of bempedoic acid among patients with and without diabetes: prespecified analysis of the CLEAR Outcomes randomised trial. Lancet Diabetes Endocrinol. 2024;12(1):19–28.
10. Henney NC, Banach M, Penson PE. RNA silencing in the management of dyslipidemias. Curr Atheroscler Rep. 2021;23(11):69. https://doi.org/10.1007/s11883-021-00968-7.
11. Surma S, Shapiro MD, Banach M. Breaking new ground in lipid management: Insights from the 2024 American College of Cardiology Scientific Sessions. Pharmacol Res. 2024;205: 107246.
12. Robinson JG, et al. Enhancing the value of PCSK9 monoclonal antibodies by identifying patients most likely to benefit. A consensus statement from the National Lipid Association. J Clin Lipidol. 2019; 13(4):525–537.
13. Boren J, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2020;41(24):2313–30.
14. Ning H, Perak AM, Siddique J, Wilkins JT, Lloyd-Jones DM, Allen NB. Association between life's essential 8 cardiovascular health metrics with cardiovascular events in the cardiovascular disease lifetime risk pooling project. Circ Cardiovasc Qual Outcomes. 2024;19: e010568. https://doi.org/10.1161/CIRCOUTCOMES.123.010568.
15. Serban MC, et al. Statin intolerance and risk of coronary heart events and all-cause mortality following myocardial infarction. J Am Coll Cardiol. 2017;69(11):1386–95.
16. Banach M, Penson PE. Adherence to statin therapy: it seems we know everything, yet we do nothing. Eur Heart J Open. 2022;2(6):oeac071. https://doi.org/10.1093/ehjopen/oeac071.
17. Ray KK, Haq I, Bilitou A, Manu MC, Burden A, Aguiar C, Arca M, Connolly DL, Eriksson M, Ferrières J, Laufs U, Mostaza JM, Nanchen D, Rietzschel E, Strandberg T, Toplak H, Visseren FLJ, Catapano AL; SANTORINI Study Investigators. Treatment gaps in the implementation of LDL cholesterol control among high- and very high-risk patients in Europe between 2020 and 2021: the multinational observational SANTORINI study. Lancet Reg Health Eur. 2023; 29:100624. https://doi.org/10.1016/j.lanepe.2023.100624.
18. Schubert J, et al. Low-density lipoprotein cholesterol reduction and statin intensity in myocardial infarction patients and major adverse outcomes: a Swedish nationwide cohort study. Eur Heart J. 2021;42(3):243–52.
19. Lee SJ, Joo JH, Park S, Kim C, Choi DW, Hong SJ, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, Jang Y, Nam CM, Hong MK. Combination lipid-lowering therapy in patients undergoing percutaneous coronary intervention. J Am Coll Cardiol. 2023;82(5):401–10. https://doi.org/10.1016/j.jacc.2023.05.042.

20. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan GA, Dweck MR, Galbraith M, Gilard M, Hinterbuchner L, Jankowska EA, Jüni P, Kimura T, Kunadian V, Leosdottir M, Lorusso R, Pedretti RFE, Rigopoulos AG, Rubini Gimenez M, Thiele H, Vranckx P, Wassmann S, Wenger NK, Ibanez B; ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023; 44(38):3720–3826.
21. Visseren FLJ, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227–337.
22. Mach F, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88.
23. Dyrbus K, et al. Risk-factors associated with extremely high cardiovascular risk of mid- and long-term mortality following myocardial infarction: analysis of the Hyperlipidaemia Therapy in tERtiary Cardiological cEnTer (TERCET) registry. Atherosclerosis. 2021;333:16–23.
24. Banach M, et al. Optimal use of lipid-lowering therapy after acute coronary syndromes: a position paper endorsed by the International Lipid Expert Panel (ILEP). Pharmacol Res. 2021;166: 105499.
25. Ray KK, Reeskamp LF, Laufs U, Banach M, Mach F, Tokgözoğlu LS, Connolly DL, Gerrits AJ, Stroes ESG, Masana L, Kastelein JJP. Combination lipid-lowering therapy as first-line strategy in very high-risk patients. Eur Heart J. 2022;43(8):830–3.
26. Penson PE, et al. Step-by-step diagnosis and management of the nocebo/drucebo effect in statin-associated muscle symptoms patients: a position paper from the International Lipid Expert Panel (ILEP). J Cachexia Sarcopenia Muscle. 2022;13(3):1596–622.
27. Paponja K, Pećin I, Reiner Ž, Banach M. Bempedoic acid: new evidence and recommendations on use. Curr Opin Lipidol. 2024;35(1):41–50.
28. Banach M, et al. Personalized management of dyslipidemias in patients with diabetes-it is time for a new approach. Cardiovasc Diabetol. 2022;21(1):263.
29. Banach M, Surma S, Kapłon-Cieślicka A, Mitkowski P, Dzida G, Tomasik T, et al. Position paper of the Polish expert group on the use of pitavastatin in the treatment of lipid disorders in Poland endorsed by the Polish Lipid Association. Lekarz POZ. 2023;9(6):309–26.
30. Sosnowska B, Stepinska J, Mitkowski P, Bielecka-Dabrowa A, Bobrowska B, Budzianowski J, Burchardt P, Chlebus K, Dobrowolski P, Gasior M, Jankowski P, Kubica J, Mickiewicz A, Mysliwiec M, Osadnik T, Prejbisz A, Rajtar-Salwa R, Wita K, Witkowski A, Gil R, Banach M. Recommendations of the Experts of the Polish Cardiac Society (PCS) and the Polish Lipid Association (PoLA) on the diagnosis and management of elevated lipoprotein(a) levels. Arch Med Sci. 2024;20(1):8–27.
31. Lewek J, Niedziela J, Desperak P, Dyrbuś K, Osadnik T, Jankowski P, Witkowski A, Bielecka-Dąbrowa A, Dudek D, Gierlotka M, Gąsior M, Banach M. Intensive statin therapy versus upfront combination therapy of statin and ezetimibe in patients with acute coronary syndrome: a propensity score matching analysis based on the PL-ACS data. J Am Heart Assoc. 2023;12(18): e030414.
32. Banach M, Reiner Z, Cicero AFG, Sabouret P, Viigimaa M, Sahebkar A, Postadzhiyan A, Gaita D, Pella D, Penson PE. 2022: the year in cardiovascular disease - the year of upfront lipid lowering combination therapy. Arch Med Sci. 2022;18(6):1429–34.
33. Ray KK, et al. EU-wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study. Eur J Prev Cardiol. 2021;28(11):1279–89.
34. Vrablik M, Seifert B, Parkhomenko A, Banach M, Jóźwiak JJ, Kiss RG, Gaita D, Rašlová K, Zachlederova M, Bray S, Ray KK. Lipid-lowering therapy use in primary and secondary care in Central and Eastern Europe: DA VINCI observational study. Atherosclerosis. 2021;334:66–75.
35. Lin I, et al. Patterns of statin use in a real-world population of patients at high cardiovascular risk. J Manag Care Spec Pharm. 2016;22(6):685–98.
36. Nowowiejska-Wiewióra A, Wita K, Mędrala Z, Tomkiewicz-Pająk L, Bujak K, Mizia-Stec K, Brzychczy P, Gąsior M, Gąsior Z, Kulbat A, Kalarus Z, Wojakowski W, Trzeciak P, Witkowski A, Banach M, Legutko J. Dyslipidemia treatment and attainment of LDL-cholesterol treatment goals in patients participating in the Managed Care for Acute Myocardial Infarction Survivors program. Kardiol Pol. 2023;81(4):359–65.
37. Kim BK, Hong SJ, Lee YJ, Hong SJ, Yun KH, Hong BK, Heo JH, Rha SW, Cho YH, Lee SJ, Ahn CM, Kim JS, Ko YG, Choi D, Jang Y, Hong MK; RACING investigators. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. Lancet. 2022;400(10349):380–390.
38. Lee YJ, Cho JY, You SC, Lee YH, Yun KH, Cho YH, Shin WY, Im SW, Kang WC, Park Y, Lee SY, Lee SJ, Hong SJ, Ahn CM, Kim BK, Ko YG, Choi D, Hong MK, Jang Y, Kim JS. Moderate-intensity statin with ezetimibe vs. high-intensity statin in patients with diabetes and atherosclerotic cardiovascular disease in the RACING trial. Eur Heart J. 2023;44(11):972–983.
39. Lee SH, Lee YJ, Heo JH, Hur SH, Choi HH, Kim KJ, Kim JH, Park KH, Lee JH, Choi YJ, Lee SJ, Hong SJ, Ahn CM, Kim BK, Ko YG, Choi D, Hong MK, Jang Y, Kim JS. Combination moderate-intensity statin and ezetimibe therapy for elderly patients with atherosclerosis. J Am Coll Cardiol. 2023;81(14):1339–49.
40. Lee SJ, Joo JH, Park S, Kim C, Choi DW, Lee YJ, Hong SJ, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, Jang Y, Nam CM, Hong MK. Combination therapy with moderate-intensity atorvastatin and ezetimibe versus high-intensity atorvastatin monotherapy in patients treated with percutaneous coronary intervention in practice: assessing RACING generalizability. Eur Heart J Cardiovasc Pharmacother. 2023. https://doi.org/10.1093/ehjcvp/pvad083.
41. Banach M. The upfront lipid-lowering combination therapy of statins and ezetimibe vs statin monotherapy in the reduction of cardiovascular outcomes. A meta-analysis. Presentation at the ESC Congress 2024 in London, 30th Aug 2024. https://esc365.escardio.org/presentation/287273
42. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003;326(7404):1419.
43. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/pcna guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol. 2019;73(24):3168–209.
44. Banach M, Burchardt P, Chlebus K, Dobrowolski P, Dudek D, Dyrbuś K, Gąsior M, Jankowski P, Jóźwiak J, Kłosiewicz-Latoszek L, Kowalska I, Małecki M, Prejbisz A, Rakowski M, Rysz J, Solnica B, Sitkiewicz D, Sygitowicz G, Sypniewska G, Tomasik T, Windak A, Zozulińska-Ziółkiewicz D, Cybulska B. PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021. Arch Med Sci. 2021;17(6):1447–547.
45. Katzmann JL, et al. Non-statin lipid-lowering therapy over time in very-high-risk patients: effectiveness of fixed-dose statin/

ezetimibe compared to separate pill combination on LDL-C. Clin Res Cardiol. 2022;111(3):243–52.
46. Penson P, McGowan M, Banach M. Evaluating bempedoic acid for the treatment of hyperlipidaemia. Expert Opin Investig Drugs. 2017;26(2):251–9.
47. Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJP, Thompson PD, Libby P, Cho L, Plutzky J, Bays HE, Moriarty PM, Menon V, Grobbee DE, Louie MJ, Chen CF, Li N, Bloedon L, Robinson P, Horner M, Sasiela WJ, McCluskey J, Davey D, Fajardo-Campos P, Petrovic P, Fedacko J, Zmuda W, Lukyanov Y, Nicholls SJ; CLEAR Outcomes investigators. bempedoic acid and cardiovascular outcomes in statin-intolerant patients. N Engl J Med. 2023;388(15):1353–1364.
48. Cicero AFG, Fogacci F, Hernandez AV, Banach M; Lipid and Blood Pressure Meta-Analysis Collaboration (LBPMC) Group and the International Lipid Expert Panel (ILEP). Efficacy and safety of bempedoic acid for the treatment of hypercholesterolemia: a systematic review and meta-analysis. PLoS Med. 2020;17(7):e1003121.
49. Leiter LA, Banach M, Catapano AL, Duell PB, Gotto AM Jr, Laufs U, Mancini GBJ, Ray KK, Hanselman JC, Ye Z, Bays HE. Bempedoic acid in patients with type 2 diabetes mellitus, prediabetes, and normoglycaemia: a post hoc analysis of efficacy and glycaemic control using pooled data from phase 3 clinical trials. Diabetes Obes Metab. 2022;24(5):868–80.
50. Nicholls SJ, Nelson AJ, Lincoff AM, Brennan D, Ray KK, Cho L, Menon V, Li N, Bloedon L, Nissen SE. Impact of bempedoic acid on total cardiovascular events: a prespecified analysis of the CLEAR outcomes randomized clinical trial. JAMA Cardiol. 2024;9(3):245–53.
51. Stroes ESG, Bays HE, Banach M, Catapano AL, Duell PB, Laufs U, Mancini GBJ, Ray KK, Sasiela WJ, Zhang Y, Gotto AM Jr. Bempedoic acid lowers high-sensitivity C-reactive protein and low-density lipoprotein cholesterol: analysis of pooled data from four phase 3 clinical trials. Atherosclerosis. 2023;373:1–9.
52. Ridker PM, Lei L, Louie MJ, Haddad T, Nicholls SJ, Lincoff AM, Libby P, Nissen SE; CLEAR Outcomes Investigators. Inflammation and cholesterol as predictors of cardiovascular events among 13,970 contemporary high-risk patients with statin intolerance. Circulation. 2024;149(1):28–35.
53. Nissen SE, Menon V, Nicholls SJ, Brennan D, Laffin L, Ridker P, Ray KK, Mason D, Kastelein JJP, Cho L, Libby P, Li N, Foody J, Louie MJ, Lincoff AM. Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients. JAMA. 2023;330(2):131–40.
54. Banach M, Surma S, Kapłon-Cieślicka A, Mitkowski P, Dzida G, Tomasik T, Mastalerz-Migas A. Position paper of the Polish Expert Group on the use of pitavastatin in the treatment of lipid disorders in Poland endorsed by the Polish Lipid Association. Arch Med Sci. 2023;20(1):28–42.
55. Watts GF, Gidding SS, Hegele RA, Raal FJ, Sturm AC, Jones LK, Sarkies MN, Al-Rasadi K, Blom DJ, Daccord M, de Ferranti SD, Folco E, Libby P, Mata P, Nawawi HM, Ramaswami U, Ray KK, Stefanutti C, Yamashita S, Pang J, Thompson GR, Santos RD. International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia. Nat Rev Cardiol. 2023;20(12):845–69.
56. Sahebkar A, et al. A comprehensive review on the lipid and pleiotropic effects of pitavastatin. Prog Lipid Res. 2021;84: 101127.
57. Grinspoon SK, Fitch KV, Zanni MV, Fichtenbaum CJ, Umbleja T, Aberg JA, Overton ET, Malvestutto CD, Bloomfield GS, Currier JS, Martinez E, Roa JC, Diggs MR, Fulda ES, Paradis K, Wiviott SD, Foldyna B, Looby SE, Desvigne-Nickens P, Alston-Smith B, Leon-Cruz J, McCallum S, Hoffmann U, Lu MT, Ribaudo HJ, Douglas PS; REPRIEVE Investigators. Pitavastatin to prevent cardiovascular disease in HIV infection. N Engl J Med. 2023;389(8):687–699.
58. Lu MT, Ribaudo H, Foldyna B, Zanni MV, Mayrhofer T, Karady J, Taron J, Fitch KV, McCallum S, Burdo TH, Paradis K, Hedgire SS, Meyersohn NM, DeFilippi C, Malvestutto CD, Sturniolo A, Diggs M, Siminski S, Bloomfield GS, Alston-Smith B, Desvigne-Nickens P, Overton ET, Currier JS, Aberg JA, Fichtenbaum CJ, Hoffmann U, Douglas PS, Grinspoon SK; REPRIEVE Trial Writing Group. Effects of pitavastatin on coronary artery disease and inflammatory biomarkers in HIV: mechanistic substudy of the REPRIEVE randomized clinical trial. JAMA Cardiol. 2024;9(4):323–334.
59. Cholesterol Treatment Trialists' Collaboration. Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials: an individual participant data meta-analysis. Lancet Diabetes Endocrinol. 2024;12(5):306–19.
60. Katsiki N, Vrablik M, Banach M, Gouni-Berthold I. Inclisiran, low-density lipoprotein cholesterol and lipoprotein (a). Pharmaceuticals (Basel). 2023;16(4):577.
61. Ray KK, Troquay RPT, Visseren FLJ, Leiter LA, Scott Wright R, Vikarunnessa S, Talloczy Z, Zang X, Maheux P, Lesogor A, Landmesser U. Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial. Lancet Diabetes Endocrinol. 2023;11(2):109–19.
62. Wright RS, Raal FJ, Koenig W, Landmesser U, Leiter LA, Vikarunnessa S, Lesogor A, Maheux P, Talloczy Z, Zang X, Schwartz GG, Ray KK. Inclisiran administration potently and durably lowers LDL-C over an extended-term follow-up: the ORION-8 trial. Cardiovasc Res. 2024. https://doi.org/10.1093/cvr/cvae109.
63. Wright RS, Koenig W, Landmesser U, Leiter LA, Raal FJ, Schwartz GG, Lesogor A, Maheux P, Stratz C, Zang X, Ray KK. Safety and tolerability of inclisiran for treatment of hypercholesterolemia in 7 clinical trials. J Am Coll Cardiol. 2023;82(24):2251–61.
64. Koren MJ, Rodriguez F, East C, Toth PP, Watwe V, Abbas CA, Sarwat S, Kleeman K, Kumar B, Ali Y, Jaffrani N. An inclisiran first strategy vs usual care in patients with atherosclerosis. J Am Coll Cardiol. 2024;83(20):1939–52.
65. Ray KK, Raal FJ, Kallend DG, Jaros MJ, Koenig W, Leiter LA, Landmesser U, Schwartz GG, Lawrence D, Friedman A, Garcia Conde L, Wright RS; ORION Phase III investigators. Inclisiran and cardiovascular events: a patient-level analysis of phase III trials. Eur Heart J. 2023 ;44(2):129–138.
66. Bytyci I, et al. Prevalence of statin intolerance: a meta-analysis. Eur Heart J. 2022;43(34):3213–23.
67. Banach M. Statin intolerance: time to stop letting it get in the way of treating patients. Lancet. 2022;400(10355):791–3. https://doi.org/10.1016/S0140-6736(22)01643-9.
68. Cholesterol Treatment Trialists' Collaboration. Effect of statin therapy on muscle symptoms: an individual participant data meta-analysis of large-scale, randomised, double-blind trials. Lancet. 2022;400(10355):832-845.
69. Ruscica M, Ferri N, Banach M, Sirtori CR, Corsini A. Side effects of statins: from pathophysiology and epidemiology to diagnostic and therapeutic implications. Cardiovasc Res. 2023;118(17):3288–304.
70. Banach M, Shekoohi N, Mikhailidis DP, Lip GYH, Hernandez AV, Mazidi M. Relationship between low-density lipoprotein cholesterol, lipid-lowering agents and risk of stroke: a meta-analysis of observational studies (n = 355,591) and randomized controlled trials (n = 165,988). Arch Med Sci. 2022;18(4):912–29.

71. Sabouret P, Angoulvant D, Cannon CP, Banach M. Low levels of low-density lipoprotein cholesterol, intracerebral haemorrhage, and other safety issues: is there still a matter of debate? Eur Heart J Open. 2022;2(4):oeac038.
72. Goldstein LB, Toth PP, Dearborn-Tomazos JL, Giugliano RP, Hirsh BJ, Peña JM, Selim MH, Woo D; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Peripheral Vascular Disease; and Stroke Council. Aggressive LDL-C lowering and the brain: impact on risk for dementia and hemorrhagic stroke: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol. 2023; 43(10):e404–e442.
73. Banach M, Cannon CP, Paneni F, Penson PE; endorsed by the International Lipid Expert Panel (ILEP). Individualized therapy in statin intolerance: the key to success. Eur Heart J. 2023;44(7):544–546.
74. Penson PE, Pirro M, Banach M. LDL-C: lower is better for longer-even at low risk. BMC Med. 2020;18(1):320.
75. Cybulska B, et al. How much should LDL cholesterol be lowered in secondary prevention? Clinical efficacy and safety in the era of PCSK9 inhibitors. Prog Cardiovasc Dis. 2021;67:65–74.
76. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Borén J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgözoglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38(32):2459–2472.
77. Banach M, Penson PE. Lipid-lowering therapies: better together. Atherosclerosis. 2021;320:86–8.
78. Banach M, Penson PE. Statins and LDL-C in secondary prevention-so much progress, so far to go. JAMA Netw Open. 2020;3(11): e2025675.
79. National Institute for Health and Care Excellence (NICE), TA733: Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia. 2021.
80. Mitkowski P, Witkowski A, Stępińska J, Banach M, Jankowski P, Gąsior M, Wita K, Bartuś S, Burchardt P, Farkowski MM, Gierlotka M, Gil R, Leszek P, Sterliński M, Szymański P, Tajstra M, Tycińska A, Wojakowski W. Position of the Polish Cardiac Society on therapeutic targets for LDL cholesterol concentrations in secondary prevention of myocardial infarctions. Kardiol Pol. 2023;81(7–8):818–23.
81. Gaudet D, et al. Safety and efficacy of alirocumab in a real-life setting: the ODYSSEY APPRISE study. Eur J Prev Cardiol. 2022;28(17):1864–72.
82. Banach M, Lewek J, Pol K, Rabczenko D, Balanescu SM, Blaha V, Ceska R, Jankowski P, Surma S, Kolovou G, Liberopoulos E, Mitu F, Mitu M, Naji FH, Paragh G, Popławska M, Vrablik M, Pella D. Regional differences in physicians' behavior and factors influencing the intensity of PCSK9 inhibitor therapy with alirocumab: a subanalysis of the ODYSSEY APPRISE study. Front Cardiovasc Med. 2023;10:1206551.
83. Nissen SE. Statin denial: an internet-driven cult with deadly consequences. Ann Intern Med. 2017;167(4):281–2.
84. Penson PE, Banach M. Nocebo/drucebo effect in statin-intolerant patients: an attempt at recommendations. Eur Heart J. 2021;42(47):4787–8.
85. Katsiki N, et al. Statin loading in cardiovascular surgery: never too early to treat. Curr Opin Cardiol. 2018;33(4):436–43.
86. Wita K, et al. Managed care after acute myocardial infarction (MC-AMI) reduces total mortality in 12-month follow-up-results from a poland's national health fund program of comprehensive post-MI Care-a population-wide analysis. J Clin Med. 2020;9(10):3178.
87. Jankowski P, Topór-Mądry R, Gąsior M, Cegłowska U, Eysymontt Z, Gierlotka M, Wita K, Legutko J, Dudek D, Sierpiński R, Pinkas J, Kaźmierczak J, Witkowski A, Szumowski Ł. Innovative managed care may be related to improved prognosis for acute myocardial infarction survivors. Circ Cardiovasc Qual Outcomes. 2021;14(8): e007800.
88. Diaz R, et al. Intensity of statin treatment after acute coronary syndrome, residual risk, and its modification by alirocumab: insights from the ODYSSEY OUTCOMES trial. Eur J Prev Cardiol. 2021;28(1):33–43.
89. Banach M, Penson PE. What have we learned about lipids and cardiovascular risk from PCSK9 inhibitor outcome trials: ODYSSEY and FOURIER? Cardiovasc Res. 2019;115(3):e26–31.
90. Solnica B, Sygitowicz G, Sitkiewicz D, Jóźwiak J, Kasperczyk S, Broncel M, et al. 2024 Guidelines of the Polish Society of Laboratory Diagnostics and the Polish Lipid Association on laboratory diagnostics of lipid metabolism disorders. Arch Med Sci. 2024;20(2):357–74. https://doi.org/10.5114/aoms/186191.
91. Reiner Z. Why might visit-to visit variability of lipoproteins have an effect on cardiovascular events? Atherosclerosis. 2020;312:99–100.
92. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023;402(10397):203–234.
93. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. Lancet. 2024;403(10431):1027–1050.
94. Gaita L, Timar B, Timar R, Fras Z, Gaita D, Banach M. Lipid Disorders Management Strategies (2024) in Prediabetic and Diabetic Patients. Pharmaceuticals (Basel). 2024;17(2):219.
95. Banach M, Surma S, Toth PP; endorsed by the International Lipid Expert Panel (ILEP). 2023: The year in cardiovascular disease - the year of new and prospective lipid lowering therapies. Can we render dyslipidemia a rare disease by 2024? Arch Med Sci. 2023;19(6):1602–1615.
96. Sabouret P, Lemesle G, Bellemain-Appaix A, Aubry P, Bocchino PP, Rafflenbeul E, Belle L, Nolan J, Bernardi M, Biondi-Zoccai G, Savage MP, Banach M, Cayla G. Post-discharge and long-term follow-up after an acute coronary syndrome: International Collaborative Group of CNCF position paper. Arch Med Sci. 2022;18(4):839–54.

Authors and Affiliations

Maciej Banach[1,2,3] · Željko Reiner[3,4] · Stanisław Surma[5] · Gani Bajraktari[6] · Agata Bielecka-Dabrowa[3] · Matjaz Bunc[7] · Ibadete Bytyçi[6] · Richard Ceska[8] · Arrigo F. G. Cicero[9] · Dariusz Dudek[10] · Krzysztof Dyrbuś[11] · Jan Fedacko[12,13] · Zlatko Fras[14,15] · Dan Gaita[16] · Dov Gavish[17] · Marek Gierlotka[18] · Robert Gil[19] · Ioanna Gouni-Berthold[20] · Piotr Jankowski[21] · Zoltán Járai[22] · Jacek Jóźwiak[23] · Niki Katsiki[24,25] · Gustavs Latkovskis[26] · Stefania Lucia Magda[27] · Eduard Margetic[28] · Roman Margoczy[29] · Olena Mitchenko[30] · Azra Durak-Nalbantic[31] · Petr Ostadal[32] · Gyorgy Paragh[33] · Zaneta Petrulioniene[34,35] · Francesco Paneni[36] · Ivan Pećin[37] · Daniel Pella[38] · Arman Postadzhiyan[39] · Anca Pantea Stoian[40] · Matias Trbusic[41] · Cristian Alexandru Udroiu[42] · Margus Viigimaa[43] · Dragos Vinereanu[27] · Charalambos Vlachopoulos[44] · Michal Vrablik[45] · Dusko Vulic[46,47] · Peter E. Penson[48,49] on behalf of International Lipid Expert Panel (ILEP)

✉ Maciej Banach
maciej.banach@iczmp.edu.pl

1 Department of Preventive Cardiology and Lipidology, Medical University of Lodz (MUL), Rzgowska 281/289, 93-338 Lodz, Poland

2 Division of Cardiology, Department of Medicine, Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, MD, USA

3 Department of Cardiology and Adult Congenital Heart Diseases, Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland

4 Division of Metabolic Diseases, Department of Internal Medicine, University Hospital Centre Zagreb, Zagreb, Croatia

5 Department of Internal Medicine and Clinical Pharmacology, Medical University of Silesia, Katowice, Poland

6 Clinic of Cardiology, University Clinical Centre of Kosova, Medical Faculty, University of Prishtina, Prishtina, Kosovo

7 Department of Cardiology, University Medical Centre Ljubljana, Ljubljana, Slovenia

8 The 3rd Department of Internal Medicine-Metabolic Care and Gerontology, Charles University and University Hospital in Hradec Králové, Hradec Králové, Czech Republic

9 Medical and Surgical Sciences Department, Alma Mater Studiorum University of Bologna, Bologna, Italy

10 Jagiellonian University Medical College, Krakow, Poland

11 3rd Department of Cardiology, School of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland

12 Department of Gerontology and Geriatric, PJ Safarik University, Kosice, Slovakia

13 MEDIPARK-University Research Park, PJ Safarik University, Kosice, Slovakia

14 Division of Medicine, Department of Vascular Medicine, Centre for Preventive Cardiology, University Medical Centre Ljubljana, Ljubljana, Slovenia

15 Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

16 Department of Cardiology, University of Medicine and Pharmacy Victor Babes, Institute of Cardiovascular Diseases, Research Center IBCVTIM, Timisoara, Romania

17 Integrated Heart Center Shaare Zedek Medical Center, Jerusalem, Israel

18 Department of Cardiology, University Hospital, Institute of Medical Sciences, University of Opole, Opole, Poland

19 Invasive Department, Centre of Postgraduate Medical Education, Warsaw, Poland

20 Faculty of Medicine and University Hospital, Center for Endocrinology, Diabetes and Preventive Medicine, University of Cologne, Cologne, Germany

21 Department of Internal Medicine and Geriatric Cardiology, Medical Centre for Postgraduate Education, Warsaw, Poland

22 Department of Cardiology, South-Buda Center Hospital, St. Imre University Teaching Hospital and Vascular and Heart Center of Semmelweis University, Budapest, Hungary

23 Department of Family Medicine and Public Health, University of Opole, Opole, Poland

24 Department of Nutritional Sciences and Dietetics, International Hellenic University, Thessaloniki, Greece

25 School of Medicine, European University Cyprus, Nicosia, Cyprus

26 Institute of Cardiology and Regenerative Medicine, University of Latvia and Pauls Stradins Clinical University Hospital, Riga, Latvia

27 University of Medicine and Pharmacy Carol Davila, University and Emergency Hospital, Bucharest, Romania

28 Clinic of Cardiovascular Diseases, University Hospital Center Zagreb, School of Medicine University of Zagreb, Zagreb, Croatia

29 Department of General Cardiology, Middle Slovak Institute of Cardiovascular Diseases, Banska Bystrica, Slovakia

30 Dyslipidaemia Department, Institute of Cardiology, AMS of Ukraine, Kiev, Ukraine

31 Clinic for Heart, Blood Vessels and Rheumatic Diseases, Medical Faculty Sarajevo, University Clinical Center Sarajevo, Sarajevo, Bosnia and Herzegovina

32 Department of Cardiology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic

33 Division of Metabolic Disease, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

[34] Faculty of Medicine, Vilnius University, Vilnius, Lithuania

[35] Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania

[36] Department of Cardiology, Center for Translational and Experimental Cardiology (CTEC), University Hospital Zurich, Zurich, Switzerland

[37] Department of Internal Medicine, School of Medicine, University of Zagreb, Zagreb, Croatia

[38] 2nd Department of Cardiology, Faculty of Medicine, Pavol Jozef Safarik University and East Slovak Institute of Cardiovascular Diseases, Kosice, Slovakia

[39] Department of General Medicine, Emergency University Hospital "St. Anna", Medical University of Sofia, Sofia, Bulgaria

[40] Department of Diabetes, Nutrition and Metabolic Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

[41] Department of Cardiology, University Hospital Centre "Sestre Milosrdnice", Zagreb, Croatia

[42] Department of Cardiology and Cardiovascular Surgery, University and Emergency Hospital, Bucharest, Romania

[43] Centre of Cardiology, North Estonia Medical Centre, Tallinn University of Technology, Tallinn, Estonia

[44] 1st Department of Cardiology, National and Kapodistrian University of Athens, Athens, Greece

[45] Third Department of Medicine-Department of Endocrinology and Metabolism of the First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

[46] Department of Internal Medicine, School of Medicine, University of Banja Luka, Banja Luka, Republic of Srpska

[47] Department of Medicine, Academy of Science and Arts, Republic of Srpska, Bosnia and Herzegovina, Banja Luka, Republic of Srpska

[48] School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK

[49] Liverpool Centre for Cardiovascular Science, Liverpool, UK