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Bempedoic acid in the management of lipid disorders and cardiovascular risk. 2023 position paper of the International Lipid Expert Panel (ILEP)

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2023 Position Paper of the International Lipid Expert Panel (ILEP)

Maciej Banach[1-4*#], Peter E. Penson[5,6#], Michel Farnier[7], Zlatko Fras[8,9], Gustavs Latkovskis[10,11], Ulrich Laufs[12], Francesco Paneni[13,14], Paolo Parini[15-17], Matteo Pirro[18], Željko Reiner[19], Michal Vrablik[20], Carlos Escobar[21]

#Drs Maciej Banach and Peter E Penson contributed equally to this paper.

[1]Department of Preventive Cardiology and Lipidology, Medical University of Lodz (MUL), Lodz, Poland; [2]Department of Cardiology and Congenital Diseases of Adults, Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland; [12]Cardiovascular Research Centre, University of Zielona Gora, Zielona Gora, Poland; [4]Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore MD, USA; [5]Clinical Pharmacy & Therapeutics Research Group, School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK; [6]Liverpool Centre for Cardiovascular Science, Liverpool, UK; [7]Physiopathology and Epidemiology Cerebro-Cardiovascular (PEC2), University of Burgundy and Franche Comté, Dijon, France; [8]Department of Vascular Disease, University Medical Center Ljubljana, Ljubljana, Slovenia; [9]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; [10]Institute of Cardiology and Regenerative Medicine, University of Latvia, Riga, Latvia; [11]Latvian Center of Cardiology, Pauls Stradins Clinical University Hospital, Riga, Latvia; [12]Klinik und Poliklinik für Kardiologie, Universitätsklinikum Leipzig, Leipzig, Germany; [13]University Heart Center, Department of Cardiology, University Hospital Zurich, Zurich, Switzerland; [14]Center for Translational and Experimental Cardiology (CTEC), University Hospital Zurich and University of Zurich, Zurich, Switzerland; [15] Cardio Metabolic Unit Department of Medicine and Department of Laboratory Medicine, Karolinska Institute, Stockholm, Sweden; [17]Medical Unit Endocrinology, Theme Inflammation and Ageing, Karolinska University Hospital, Stockholm, Sweden; [18]Unit of Internal Medicine, Angiology and Arteriosclerosis Diseases, Department of Medicine, University of Perugia, Perugia, Italy; [19]Department of Internal Diseases, University Hospital Center Zagreb, Zagreb, Croatia; [20]3rd Department of Medicine-Department of Endocrinology and Metabolism, Charles University, Prague, Czech Republic; [21]Cardiology Department, University Hospital La Paz, Madrid, Spain.

Correspondence to:
Prof. Maciej Banach, MD, PhD, FNLA, FAHA, FESC, Department of Preventive Cardiology and Lipidology, Medical University of Lodz (MUL), Rzgowska 281/289; 93-338 Lodz, Poland. Phone: +48 42 639 37 71; Fax: +48 42 639 37 71; E-mail: maciej.banach@umed.lodz.pl

ABSTRACT

Cardiovascular disease (CVD) is a chronic non-communicable disease (NCD) and the predominant cause of morbidity and mortality worldwide. Substantial reductions in the CVD prevalence have been achieved in recent years by the attenuation of risk factors (particularly hypertension and dyslipidaemias) in primary and secondary prevention. Despite the remarkable success of lipid lowering treatments, and of statins in particular, in reducing the risk of CVD, there is still an unmet clinical need for the attainment of guideline lipid-targets in even 2/3 patients.

Bempedoic acid, the first in-class inhibitor of ATP-citrate lyase presents a new approach to lipid-lowering therapy. By reducing the endogenous production of cholesterol, upstream of the rate-limiting enzyme HMG-CoA-reductase, i.e., the target of statins, bempedoic acid reduces circulating plasma concentrations of low-density lipoprotein cholesterol (LDL-C), and major adverse CVD events (MACE). Bempedoic acid has the potential to contribute to the reduction of CVD risk not only as monotherapy, but even further as part of a lipid-lowering combination therapy with ezetimibe, reducing LDL-C cholesterol up to 40%.

This position paper of the International Lipid Expert Panel (ILEP) summarises the recent evidence around the efficacy and safety of bempedoic acid and presents practical recommendations for its use, which complement the 'lower-is-better-for-longer' approach to lipid management, which is applied across international guidelines for the management of CVD risk. Practical evidence-based guidance is provided relating to the use of bempedoic acid in atherosclerotic CVD, familial hypercholesterolaemia, and statin intolerance. Although there are currently no data available for the role of bempedoic acid in the primary prevention of CVD, its favourable effects on plasma glucose and inflammatory markers makes this drug a rational choice in the patient-centred care of specific groups of primary prevention.

Keywords: Bempedoic acid, ETC1002, atherosclerotic cardiovascular disease

Alphabetical List of Abbreviations:

ACLY	adenosine triphosphate-citrate lyase
AMPK	AMP-activated protein kinase
Apo	apolipoprotein
ASCV1L	acyl-coenzyme A synthetase-1
ASCVD	Atherosclerotic Cardiovascular Disease
CEE	Central and Eastern European
CTT	Cholesterol Treatment Trialists'
CVD	Cardiovascular Disease
FDC	fixed dose combination
hsCRP	high-sensitivity C-reactive protein
ILEP	International Lipid Expert Panel
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiac event
MD	Mean Difference
MR	Mendelian randomisation
NCD	Non-communicable Disease
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PCSK9	proprotein convertase subtilisin/kexin type 9 serine protease
RCTs	randomised controlled trials
siRNA	small interference RNA
SLAP	Switch statins, Lower dose, Alternate day dosing, Polypharmacy
TEAEs	Treatment-emergent adverse events

1. Background

Cardiovascular disease (CVD) is a chronic non-communicable disease (NCD) amongst the most common causes of death worldwide. It is estimated that by 2030, 22.2 million people will die each year from CVD, an increase from 19 million in 2019[1]. Atherosclerotic CVD (ASCVD) is responsible for almost 2/3 of CVD cases, thus hypothetically most of the deaths might be preventable[1]. However, despite the bleak population statistics, substantial reductions in individual risk of CVD can be achieved through the management of modifiable risk factors, including blood pressure, and particularly low-density lipoprotein cholesterol (LDL-C)[2]. Observational studies, Mendelian randomisation (MR) studies and randomised controlled trials (RCTs) have consistently demonstrated that lifelong exposure to LDL-C is strongly associated with CVD risk, and that interventions to reduce LDL-C prevent CVD events in even 55%[3]. This underlines the importance of the concept that (with respect to LDL-C) *'lower is better for longer'.*[4]

1.1. Unmet clinical needs in lipid disorders and CVD risk

Statins inhibit the enzyme HMG-CoA-reductase, and thereby prevent accumulation of cholesterol in the body. Inhibition of cholesterol synthesis, a process that mainly take places in the liver, results in increased expression of hepatic LDL receptors and in uptake of LDL-C particles, preventing these particles from depositing in the walls of blood vessels and thereby driving atherosclerosis. Statins have proved exceptionally safe and effective in the reduction of CVD risk[5,6]. The increased recognition of the benefits of achieving very low LDL-C levels have led to consequent consecutive lowering of target LDL-C levels, making statin monotherapy (which is mostly underdosed) often insufficient to enable patients achieve their treatment LDL-C targets[7]. The Da-Vinci study, a cross-sectional evaluation of lipid-lowering therapy in primary and secondary prevention in 18 European countries, found that, among patients treated with high-intensity statin therapy, only 17% of high-risk primary prevention patients, and 22% of secondary prevention patients achieved their treatment goals[7], according to the 2019 ESC guidelines[8]. These results are even worse in the Central and Eastern European (CEE)

countries, when only 13% of high-risk patients reached the target of <55 mg/dl (1.4 mmol/L). On the other hand, only a small proportion of patients (<7%) are unable to take statin therapy without dose-limiting adverse effects (statin intolerance)[9]. As such there is a need for additional lipid lowering agents, which can be used in monotherapy, or (more effectively in combination therapy)[10] to manage CVD risk. Effective progress in lipid-lowering has been already achieved using ezetimibe (and fixed dose combination [FDC] of ezetimbe and statins), anti-proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) monoclonal antibodies (alirocumab, evolocumab)[11] and small interference RNA (siRNA, inclisiran)[12]. However, due to the fact of limited possibility of application of PCSK9 targeted approach therapy due to restrictive reimbursement criteria, there is a place in therapy for additional effective, orally available lipid-lowering drugs such as bempedoic-acid[13].

1.2. Bempedoic acid: pharmacology

Bempedoic acid is a novel lipid lowering agent which exerts its action through inhibition of the enzyme adenosine triphosphate-citrate lyase (ATC or ACLY)[13]. This results in inhibition of the mevalonate pathway of cholesterol production, upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the target of statins. Bempedoic acid is an inactive prodrug, which is activated through binding to coenzyme A, a reaction that is exclusively catalyzed by hepatic acyl-CoA synthetase-1 (ASCV1L)[13]. The hepatic activation of the drug, and its extensive first-pass metabolism result in limited exposure to the active compound in the systemic circulation[14], which explains why the drug is well-tolerated with minimal adverse effects[15,16].

1.3. Bempedoic acid: Effects on modifiable CVD risk factors

A meta-analysis of the results of ten randomised-controlled trials (n = 3,788) has provided important data on the effect of bempedoic acid on a range of CVD risk factors. Bempedoic acid therapy was associated with the significant reduction of new onset or worsening diabetes (OR 0.59; 95%CI 0.39, 0.90; p=0.01). These are summarised below (**Table 1**)[17]. Similar results were obtained in the pooled analysis of the data from phase 3 studies with bempedoic acid[18].

Table 1: Summary of the effects of bempedoic acid (180 mg/day) versus placebo on biomarkers of cardiovascular risk. OR, Odds Ratio, MD, mean difference. Data from[17]

Parameter	**Effect of bempedoic acid**	**p**
Total cholesterol	MD -14.94%; 95% CI -17.31%, -12.57%	<0.001
Non-high-density lipoprotein cholesterol	MD -18.17%; 95% CI -21.14%, -15.19%	<0.001
Low-density lipoprotein cholesterol	MD -22.94%; 95% CI -26.63%, -19.25%	<0.001
Low-density lipoprotein particle number	MD -20.67%; 95% CI -23.84%, -17.48%	<0.001
Apolipoprotein B	MD -15.18%; 95% CI -17.41%, -12.95%	<0.001
High-density lipoprotein cholesterol	MD -5.83%; 95% CI -6.14%, -5.52%	<0.001
High-density lipoprotein particle number	MD -3.21%; 95% CI -6.40%, -0.02%	0.049
hsCRP	MD -27.03%; 95% CI -31.42%, -22.64%	<0.001
Triglycerides	MD -1.51%; 95% CI -3.75%, 0.74%	0.189
Very-low-density lipoprotein particle number	MD 3.79%; 95% CI -9.81%, 17.39%	0.585
Apolipoprotein A-1	MD -1.83%; 95% CI -5.23%, 1.56%	0.290
Elevated serum uric acid	OR 3.55; 95% CI 1.03, 12.27	0.045
Elevated liver enzymes	OR 4.28; 95% CI 1.34, 13.71	0.014
Elevated creatine kinase	OR 3.79; 95% CI 1.06, 13.51	0.04

1.4. Effects of bempedoic acid on CVD outcomes

Data from 2884 patients in four phase 3 randomized, placebo-controlled trials of bempedoic acid has been applied to a validated prediction model in order to estimate the baseline 10-year risk of MACE in patients with established CVD based on measured LDL-C reduction[19]. The predicted change in 10-year CVD risk associated with bempedoic acid was estimated for each patient based on the Cholesterol Treatment Trialists' (CTT) model. In patients on high-intensity statins, the predicted reduction in absolute risk of MACE was -3.3% (-3.7% to -2.9%) and for patients on low-intensity statin therapy it was -6.0% (-7.7% to -4.3%)[19]. Modelling can never replace well-designed randomised trials; however, these data are very promising, and if confirmed, they will strongly support the use of bempedoic acid in CV risk reduction. In the meta-analysis of 6 RCTs with a total of 3956 patients and follow-ups of four to 52 weeks the authors observed numerical 16%, but not significant, difference in MACE (OR 0.84; 95%CI 0.61 to 1.15), lack of effect on all-cause mortality (OR 2.37; CI 0.80 to 6.99) and CVD mortality (OR 1.66; 95%CI 0.45 to 6.04) for bempedoic acid versus placebo was observed[20]. Bempedoic acid showed beneficial trends for non-fatal MI (OR 0.57; 95%CI 0.32 to 1.00) and was associated with a lower risk of new-onset or worsening of DM (OR 0.68; 95%CI 0.49 to 0.94)[20].

The CLEAR Outcomes study is a phase 3, double-blind, multicentre RCT comparing 180 mg bempedoic acid and placebo for the reduction of CV events in patients with statin intolerance who are at high risk for CVD and have elevated LDL-C levels[21]. The study finally enrolled 13,970 patients[22,23] (6992 were assigned to the bempedoic acid group and 6978 to the placebo group) at mean age 65.5 years (females 48.1% and 48.4% in bempedoic acid and placebo groups, respectively)[22,23] at over 1,200 sites in 32 countries. The trial was designed to be continued until 1620 patients experience a primary endpoint, with a minimum of 810 hard ischemic events (CVD death, nonfatal myocardial infarction, or nonfatal stroke) and minimum treatment duration of 36 months and a projected median treatment exposure of 42 months.[21] In a press release already in December 2022, Esperion announced that the trial had

met its primary endpoint, demonstrating statistically significant risk reduction in a 4-point major adverse CVD event (MACE) outcome in treated patients compared to control[22].

The final results of the CLEAR Outcomes study were presented at the American College of Cardiology (ACC) Congress 2023 in New Orleans. The median duration of follow-up was 40.6 months. The mean LDL-C level at baseline was 139.0 mg/dL (3.6 mmol/L) in both groups (bempedoic acid and placebo, respectively), and after 6 months, the absolute reduction in the level was greater with bempedoic acid by 29.2 mg/dl (0.76 mmol/L) (21.1%)[23]. The incidence of a primary endpoint was significantly lower by 13% with bempedoic acid than with placebo (819 patients [11.7%] vs. 927 [13.3%]; hazard ratio [HR], 0.87; 95%CI, 0.79 to 0.96; p=0.004) with absolute between-group difference in incidence 1.6% and estimated number needed to treat (NNT)=63. A composite of death from CV causes, nonfatal stroke, or nonfatal myocardial infarction was also significantly reduced with bempedoic acid by 15% (575 [8.2%] vs. 663 [9.5%]; 0.85; 95%CI, 0.76 to 0.96; p=0.006, NNT=77); fatal or nonfatal myocardial infarction by 23% (261 [3.7%] vs. 334 [4.8%]; 0.77; 95%CI, 0.66 to 0.91; P=0.002, NNT=91); and coronary revascularization by 19% (435 [6.2%] vs. 529 [7.6%]; HR0.81; 95%CI, 0.72 to 0.92; P=0.001, NNT=71) (**Figure 1**). Bempedoic acid had no significant effects on fatal or nonfatal stroke (HR 0.85, 0.67 to 1.07), death from cardiovascular causes (HR 1.04, 0.88 to 1.24), and death from any cause (HR 1.03, 0.90 to 1.18). It needs also to be mentioned that bempedoic acid significantly reduced by 34% the additional secondary endpoint of the hospitalization for unstable angina (HR 0.66, 0.50 to 0.86)[23].

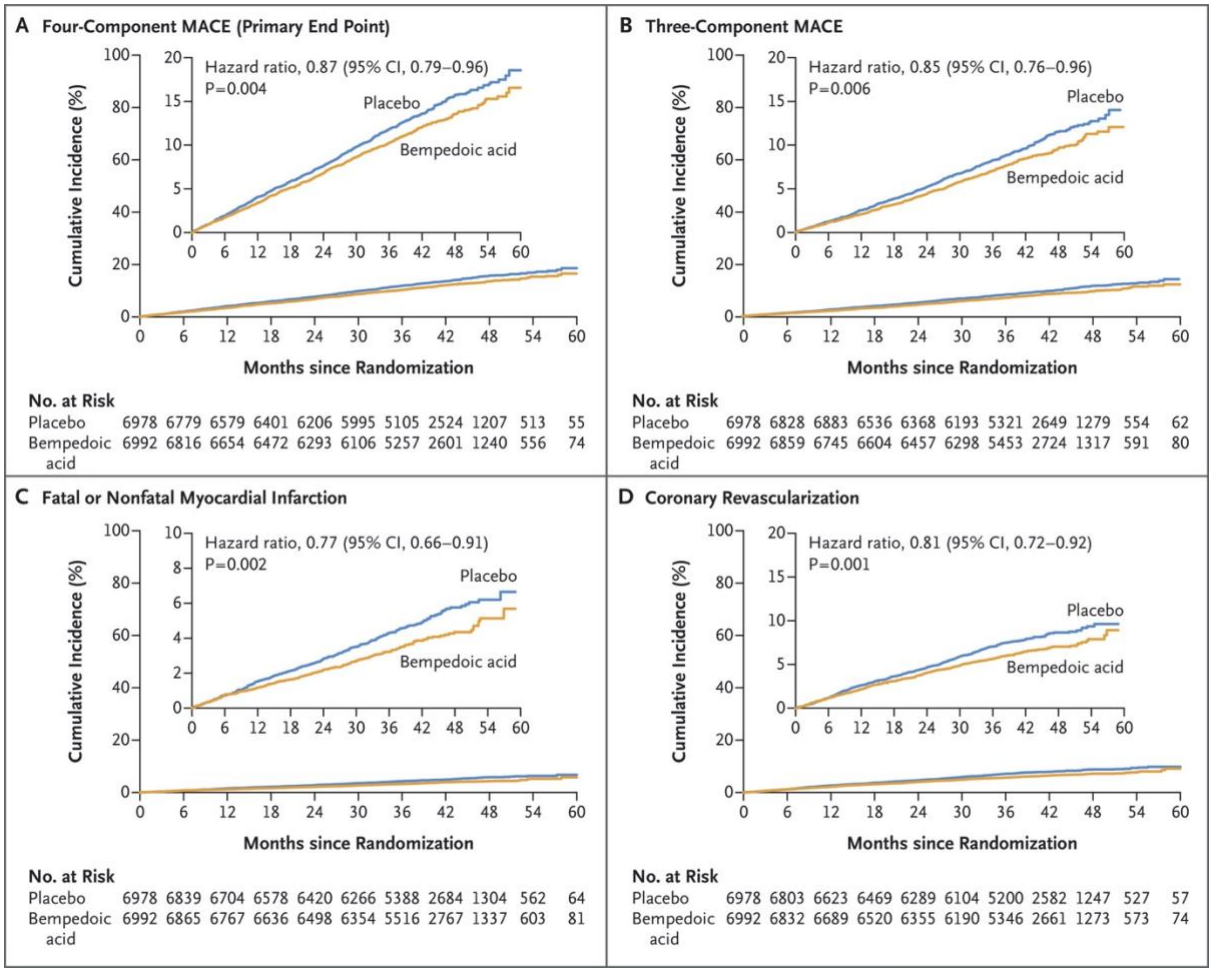

Figure 1. Cumulative Incidence of Cardiovascular Events in the Clear Outcomes study with bempedoic acid. Panel A shows the cumulative incidence of a primary end-point event, a four-component composite of MACE, defined as death from CV causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. Panel B shows the cumulative incidence of a three-component MACE, defined as death from CV causes, nonfatal myocardial infarction, or nonfatal stroke. Panel C shows the cumulative incidence of fatal or nonfatal myocardial infarction, and panel D shows the cumulative incidence of coronary revascularization. In each panel, the inset shows the same data on an enlarged y axis. The P values were calculated with the use of the log-rank test. Reprinted from [23] with the permission/licence No.: 5501990682612.

1.5. Safety of bempedoic acid

The safety of bempedoic acid has been comprehensively evaluated in a pooled analysis of 3621 patients from four, phase-three randomised-controlled trials, which measured both reported adverse effects and biochemical markers[24]. Patients (mean age 65,2±9.3 years, 66% males) were treated for a median of 363 days with 180 mg of bempedoic acid, or placebo (plus maximally tolerated statin-therapy). Treatment-emergent adverse events (TEAEs) rates (adjusted for exposure) were 87.1/100

person-years for bempedoic acid and 82.9/100 person-years for placebo[23]. Interestingly (and in contrast to most statin trials), reported incidence of muscle symptoms were similar in the treatment (1.5/100 patient years) and placebo (2.0/100 patient years) arms of the trial[23]. Additionally, the incidence of new-onset diabetes or hyperglycaemia was lower in treated patients (4.7/100 patient years), than in placebo (6.4/100 patient years)[24]. Bempedoic acid treatment appears to be associated with a small decrease in haemoglobin and small elevations of blood urea nitrogen, creatinine, and uric acid, which seem do not have any clinical relevance. In line with these observations, the incidence of gout is increased in patients treated with bempedoic acid (1.6/100 patient years) compared to placebo (0.5/100 patient years)[24]. Gout as an adverse effect of bempedoic acid treatment occurs more commonly in patients with a history of the condition, and both the symptoms and the elevated uric acid concentrations are reversible upon cessation of therapy[24]. The effect is most likely due to inhibition of the OATC2 transporter in the kidney, this pharmacologic effect is fully reversible, e.g., not mediated by toxicity[24].

Bempedoic acid is associated with a small increase in the rate of elevations of aminotransferase (to above three times greater than the upper limit of normal) – 0.8/100 patient years for bempedoic acid. compared with 0.3/100 patient years for placebo. However, this effect was transient and was reversible upon cessation of therapy[24]. Bempedoic acid therapy has been reported to be associated with an increased risk of tendon rupture, however, it should be noted that this adverse effect was only evaluated in two trials (CLEAR Harmony and CLEAR Wisdom), and that very small numbers were involved (10 patients), all of whom exhibited additional risk factors for tendon rupture (including statin use)[24]. Post-marketing surveillance of bempedoic acid is necessary for a more extensive understanding of the significance of these observations.

In the CLEAR Outcomes study the overall incidences of adverse events (AEs), serious adverse events (SAEs), and adverse events leading to discontinuation (premature discontinuation of the trial regimen was observed in 2035 patients [29.1%] in the bempedoic acid group and in 2212 patients (31.7%) in

the placebo group) did not differ meaningfully between the groups[23]. The incidences prespecified adverse events of special interest (AESI) were similar in the two trial groups except for elevations in the hepatic-enzyme level (4.5% in the bempedoic acid group vs. 3.0% in the placebo group) and renal events (11.5% in the bempedoic acid group vs. 8.6% in the placebo group; however with clinically irrelevant increases in mean creatinine level: 0.05±0.2 mg/dL with less than ≤0.6% in both groups of those with the increases of CK >5x and >10x ULN)[23]. Myalgias were reported more often in the placebo group (6.8% vs 5.6% of the patients in the bempedoic acid group). The incidence of hyperuricemia was higher in the bempedoic acid group than in the placebo group (10.9% vs. 5.6%), however with clinically irrelevant increases of uric acid (by mean 0.76±1.2 mg/dL) observed after 6 months in patients treated with bempedoic acid. The incidences of gout (3.1% vs. 2.1%) and cholelithiasis (2.2% vs. 1.2%) was also slightly increased for those treated with bempedoic acid[23]. Taking all available data on safety together, bempedoic acid appears to be safe and well-tolerated. Adverse effects are mild, reversible and treatment can be easily avoided in vulnerable patients.

1.6. Pharmaceutical formulations, licencing, and administration of bempedoic acid.

Bempedoic acid is available as 180mg film-coated tablets, and as a fixed dose combination (180mg bempedoic acid / 10mg ezetimibe). Each is taken as a single daily dose. Based on the bempedoic acid summary of product characteristics it is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated[25.] The 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk recommends the use of bempedoic acid in the management of lipids in statin intolerance[26]. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) recommends bempedoic acid with ezetimibe for the treatment of

dyslipidaemias when statins are contraindicated or not tolerated, and ezetimibe monotherapy is insufficient to achieve treatment goals[27]. The Polish 2021 guidelines on lipid management recommend considering bempedoic acid in patients with ASCVD who have not achieved the LDL-C target at their maximum tolerated dose of a statin and ezetimibe (IIb B), in FH patients at very high risk not achieving the LDL-C target with the maximum tolerated dose of a statin and ezetimibe (IIb B), and bempedoic acid or the combination of ezetimibe and bempedoic acid may be considered if a statin-based regimen is not tolerated at any dose (even after rechallenge)[28.]

2. Guideline Development Process

The International Lipid Expert Panel (ILEP; https://ilep.eu), founded in 2015 is a group of almost 90 experts representing over 50 national societies and research groups. The group serves to work together on defined projects, including the development of practical recommendations and position papers, particularly on areas of lipidology which are not comprehensively covered by the guidelines of national/ regional societies[29].

To produce these recommendations for the use of bempedoic acid in the management of lipid disorders and cardiovascular risk, a multidisciplinary Steering Committee was formed, including ILEP external recognized experts in the field. The Steering committee was chaired by Professor Maciej Banach (President and Founder of ILEP) and comprised a range of experience including cardiology, lipidology and pharmacy. The steering committee met via an extended videocall in October 2022 to critically discuss the clinical trials in which bempedoic acid had been evaluated, and to discuss suggestions for recommendations for its use in the treatment of lipid disorders and the management of cardiovascular risk.

Following the meeting, the notes and recording of the discussions were used by the Writing Committee (a subset of the Steering Committee), to formulate a draft set of recommendations. The document was circulated to the Steering Committee in advance of a second videoconference

(February 2023), in which each recommendation was discussed. Steering Committee Members decided collectively on the wording of each recommendation and on the level of each recommendation and the strength of evidence supporting it. Steering Committee members were also given the opportunity to comment on all other aspects of the texts. The amendments were included in a final draft of the manuscript, which was endorsed first by the guideline Steering Committee, then the wider ILEP community. The recommendations were completed immediately after the CLEAR Outcomes study release and the final version of the paper was again approved by all the co-authors.

3. Recommendations for the use of bempedoic acid

3.1. General principles

Treatment with bempedoic acid has significant potential to contribute to lipid target attainment, and this is likely to be in the context of combination therapy if lipid targets are to be met[10]. Bempedoic acid is available as a fixed-dose combination therapy with ezetimibe, which has an additive lipid-lowering effect (even up to 40%). Fixed-dose combinations (polypills) improve compliance with therapy and are often more cost effective than giving the same medicine in separate dosage forms[30] , therefore, the fixed-dose combination product with ezetimibe should be used.

Recommendation	**Class**	**Level**
When initiating, bempedoic acid should be used as part of a treatment strategy designed considering the patient's baseline LDL-C.	**I**	**C**
Bempedoic acid should be preferably used as a fixed-dose combination with ezetimibe.	**I**	**B**

Owing to an abundance of clinical trial data, the achievable proportional lipid-lowering effects of particular combinations of drugs is largely predictable (Error! Reference source not found. & **3**). To achieve lipid-targets in accordance with *'lower is better for longer'*, but also the '*the earlier the better'* initial combination therapy will often be preferable to starting therapy with a single drug and

adding further agents when (inevitably) the target is not met. Such an approach risks unnecessary delays to reaching target, and risks failure to escalate therapy owing to therapeutic inertia[31,32].

Figure 2 demonstrates the approximate proportional reductions in LDL-C expected with different therapeutic regimens and illustrates how these may be applied to specific patient groups.

Table 3 presents the LDL-C potential reduction of bempedoic acid in monotherapy and in combination with different lipid lowering drugs based on the available data[8,28,33], and **Table 3** applies these proportional reductions to a range of baseline LDL-concentrations to enable the selection of an appropriate therapeutic regimen.

In the context of bempedoic acid combination therapy, the manufacturer warns that concomitant use results in increased statin concentrations (even 2-fold) and increased risk of simvastatin or pravastatin-related myopathy, and that the use of bempedoic acid with doses above 20 mg of simvastatin or 40 mg of pravastatin should be avoided[22]. Summary of product characterises indicates only simvastatin 80 mg (>40 mg) as the contraindication[25]. When orally available drugs, in monotherapy or combination are unable to achieve LDL-C targets, PCSK9 targeted therapies should be considered.

Recommendation	**Class**	**Level**
Beyond statin therapy and ezetimbe, bempedoic acid should be used in combination with PCSK9 targeted therapy approach where it is necessary to achieve very large (>80%) reductions in LDL-C.	**IIa**	**C**

The International Lipid Expert Panel (ILEP) has previously outlined scenarios, in which bempedoic acid may be considered as combination therapy[31,32]. These are outlined, below (**Figure 2**).

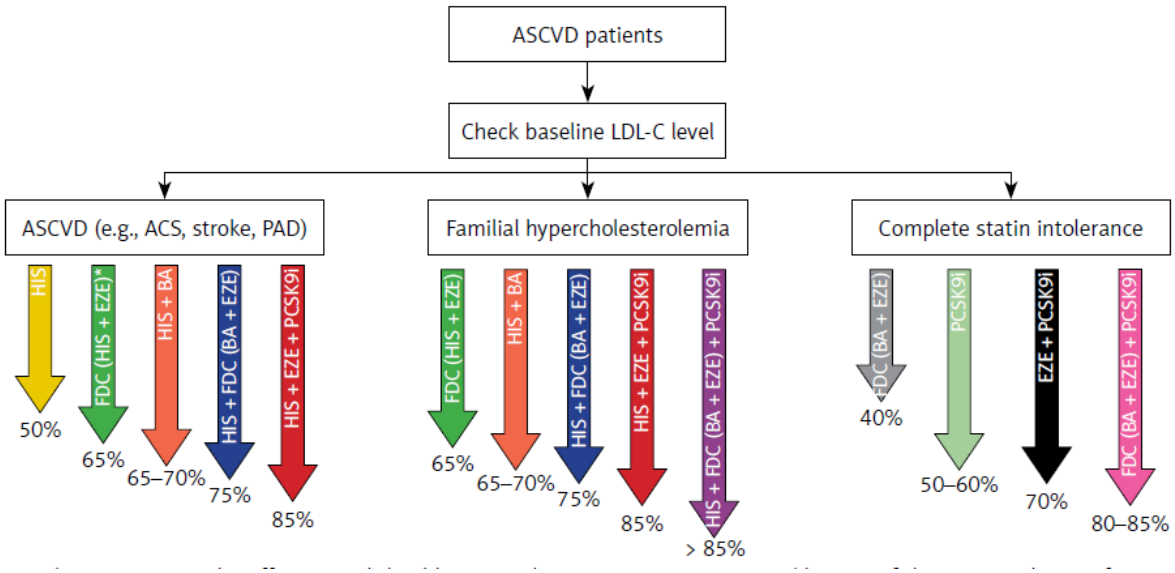

Figure 2: How to be effective with lipid lowering therapy in ASCVD patients (the size of the LDL-C reduction for some recommended combinations is an assumption and still needs to be confirmed). Reproduced with permission from [31].

Table 2. LDL-C potential reduction of bempedoic acid in monotherapy and in combination with different lipid lowering drugs based on the available data (the size of the LDL-C reduction for some recommended combinations is an assumption and still needs to be confirmed).

Treatment	**LDL-C reduction (%)**
Bempedoic acid	17-27%
- in statin-naïve patients	~25%
- on top of statins	~18%
Ezetimibe + bempedoic acid	38%
- in statin-naïve patients	~40%
- on top of statins	~35%
Low-intensity statin + bempedoic acid	~40-45%
Low-intensity statin + ezetimibe + bempedoic acid	~55-60%
Moderate-intensity statin + bempedoic acid	~50-55%
Moderate-intensity statin + ezetimibe + bempedoic acid	64%
High-intensity statins + bempedoic acid	~65%
High-intensity statins + ezetimibe + bempedoic acid	~70-75%

Ezetimibe + bempedoic acid + PCSK9 targeted therapy approach	80-85%
High-intensity statins + ezetimibe + bempedoic acid + PCSK9 targeted therapy approach	>85%

Table 3: Baseline LDL-C concentrations and % reduction required to reach treatment targets (55 mg/dl/1.4 mmol/L). FDC, Fixed dose combination.

Baseline LDL-C mg/dl (mmol/L)	**Reduction required (%)**	**Therapeutic regimens**
90-100 (2.3-2.6)	40%	FDC (bempedoic acid + ezetimibe)
<110 (2.8)	50%	High-intensity statin
110-160 (2.8-4.1)	65%	FDC (High-intensity statin + ezetimibe)
110-185 (2.8-4.8)	65-70%	High intensity statin + bempedoic acid
160-220 (4.1-5.7)	75%	High intensity statin + FDC (bempedoic acid + ezetimibe)
220-370 (5.7-9.6)	85%	High intensity statin + ezetimibe + PCSK9 targeted approach therapy
400 (10.3)	>85%	High intensity statin + FDC (bempedoic acid + ezetimibe) + PCSK9 targeted approach therapy

3.2. ASCVD

In patients with ASCVD, it is essential to early and optimally manage risk factors to prevent subsequent cardiovascular events, however target attainment is poor[7,8] owing to clinical inertia, under-prescribing, and poor adherence to therapy. International Lipid Expert Panel Recommendations have emphasised the importance of initial combination therapy and treatment escalation to achieve therapeutic targets[32]. For details on how to proceed with ASCVD patients with bempedoic acid see **Figure 2**.

Recommendation	Class	Level
Bempedoic acid is recommended in combination with statins and other lipid-lowering drugs in atherosclerotic disease when the LDL-C treatment targets are not met. The initial treatment strategy should be designed considering the patient's baseline LDL-C.	**I**	**A**

3.3. Heterozygous familial hypercholesterolaemia

In heterozygous familial hypercholesterolaemia, large and sustained reductions of LDL-C are necessary to reduce lifetime risk of cardiovascular risk.[34-37] The available phase-3 studies confirmed the beneficial role of the bempedoic acid in these patients[18,38], including also long-term studies with follow-up up to 130 weeks[39]. For details on how to proceed with heFH patients with bempedoic acid see **Figure 2**.

Recommendation	Class	Level
Bempedoic acid is recommended in combination with statins and other lipid-lowering drugs in heterozygous familial hypercholesterolaemia when the LDL-C treatment targets are not met. The initial treatment strategy should be designed considering the patient's baseline LDL-C.	**I**	**A**

3.4. Statin Intolerance

The International Lipid Expert Panel in 2022 has produced detailed guidance for the management of statin intolerance[40] **(Figure**). Bempedoic acid has a role in the 'polypharmacy' element of the SLAP (*Switch* statins, *Lower dose, Alternate day dosing*, *Polypharmacy*) algorithm to manage lipids in the presence of statin intolerance[40,41]. Phase-3 trials and recently published CLEAR Outcomes study[23] with bempedoic acid confirmed its beneficial properties and safety in statin intolerant patients, with higher

effectiveness in LDL-C reduction in comparison to those treated with maximally tolerated statins[42-44]. For details on how to proceed with statin intolerant patients with bempedoic acid see **Figure 2**.

Recommendation	**Class**	**Level**
In partial statin intolerance, combination therapy with bempedoic acid is recommended in combination with maximally tolerated statins and other non-statin agents to enable patients to reach therapeutic goals.	**I**	**A**

In complete statin intolerance bempedoic acid in monotherapy but particularly in a fixed-dose combination (FDC) with ezetimibe (or in combination with other lipid-lowering drugs) is recommended. However, if oral non-statin drugs do not result in achievement of therapeutic targets, PCSK9 targeted therapy approach should be considered. Both groups of patients with statin intolerance were highly represented in the CLEAR Outcomes study (with 22.9% of those with partial statin intolerance), which confirmed high efficacy and safety of bempedoic acid in these patients[23].

Recommendation	**Class**	**Level**
In complete statin intolerance, bempedoic acid in monotherapy or in combination with ezetimibe (FDC) and other non-statin drugs is recommended to enable patients to reach their therapeutic goals.	**I**	**A**

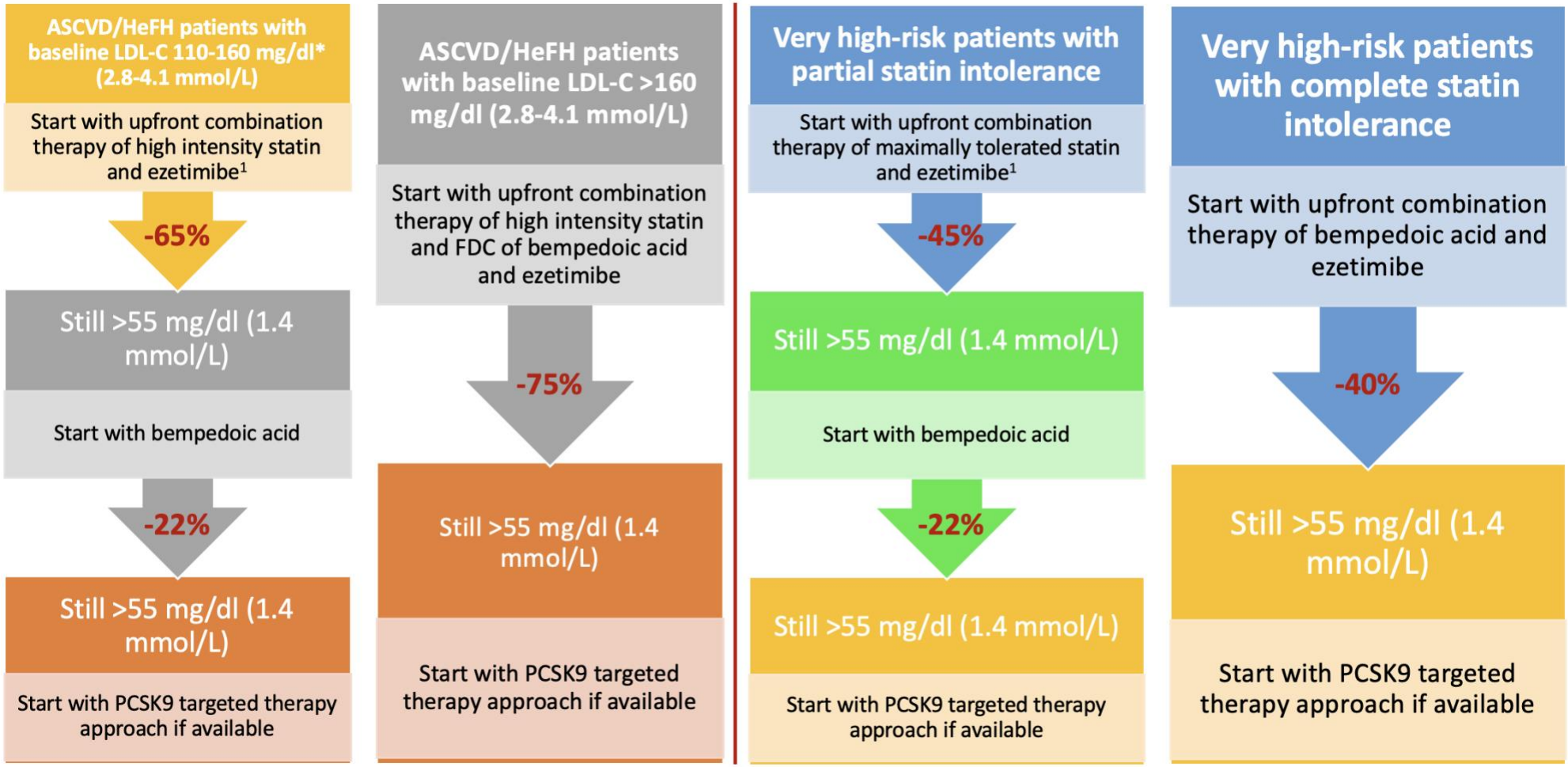

Figure 3: ILEP recommended pathways on the application of bempedoic acid in different groups of patients at very high cardiovascular risk. [1]Preferably as fixed dose combination (FDC). *In heFH patients LDL-C level between 110-160 mg/dl (2.8-4.1 mmol/L) is observed relatively rare.

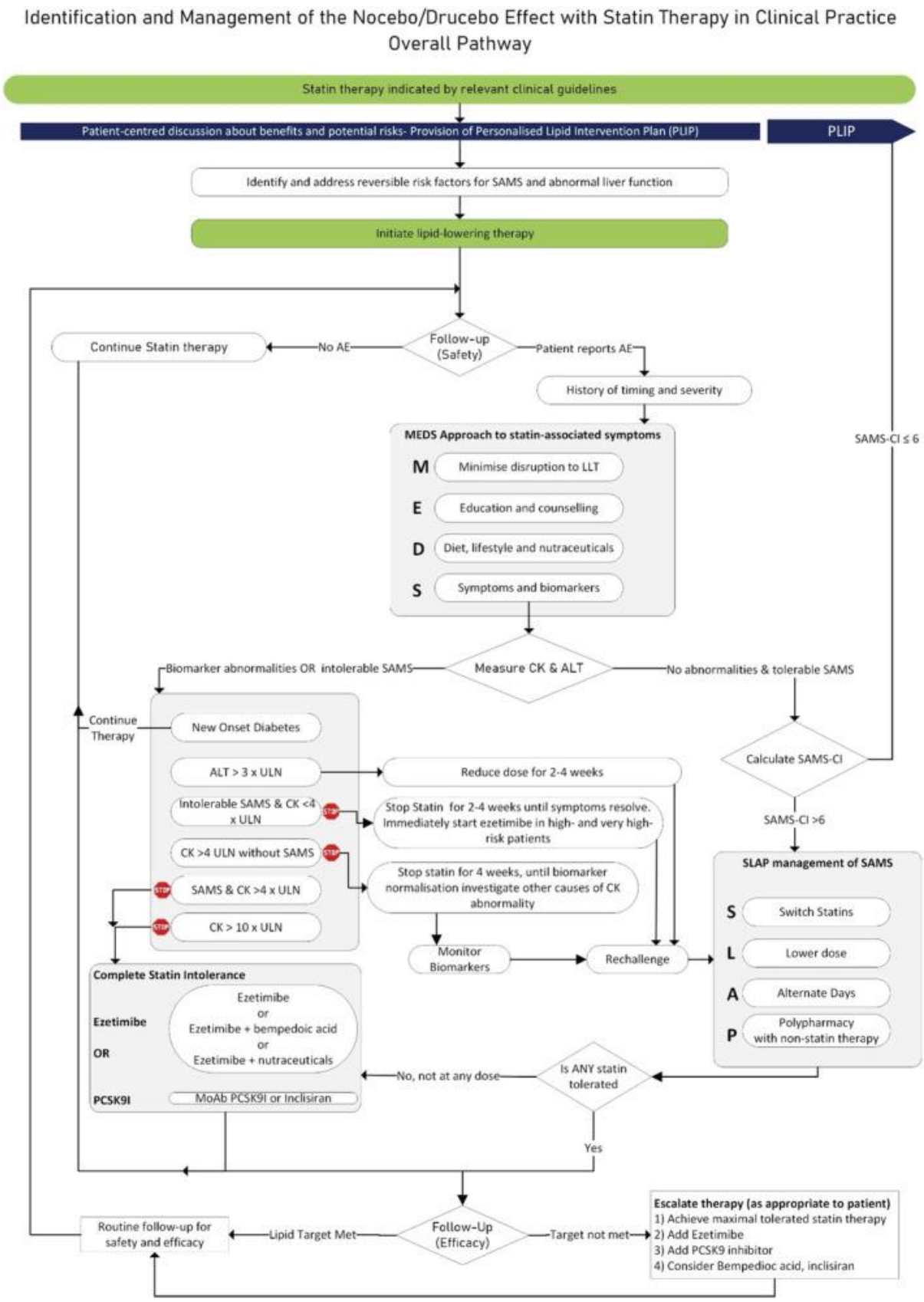

Figure 4: The International Lipid Expert Panel pathway for the management of statin intolerance. With permission from [40].

4. Patient-centred considerations for the use of bempedoic acid, and potential use in primary prevention

Whilst there are no current phase 3 and outcomes trials investigating the role of bempedoic acid in the primary prevention of CVD, the lipid-independent effects of the drug raise the possibility of particular situations in which bempedoic acid may be a rational choice of agent to include in the therapeutic regimen. The CLEAR Outcomes study was the first to evaluate the efficacy of bempedoic acid in primary prevention patients with statin intolerance as a subpopulation (30% of primary prevention patients at high and very high cardiovascular risk were included in each study group), showing significant reduction of the primary composite endpoint (HR 0.68, 95%Cl: 0,53-0,87)[23]. However, it needs to be emphasized that the number of events observed in these patients was low (n=111 for bempedoic acid), therefore we cannot treat these results as conclusive[23]. We still require dedicated studies in primary prevention with bempedoic acid in high and very high-risk patients treated optimally with statins and ezetimbe, to show the final benefit of bempedoic acid as an add-on therapy both in the relation to LDL-C goals achievement and reduction of CV events.

The experts of these recommendations are aware that in primary prevention therapy based on highly available and cheap drugs like statins and ezetimibe should result in even 80% of the patients on LDL-C target, but due to extreme statin underdosing and underutilization of the combination therapy of statin and ezetimibe, this is only a hypothetical assumption[7,31,32,45,46]. Thus, we should look for the new non-statin drugs also in primary prevention like bempedoic acid, PCSK9 inihibitors that are already in the guidelines in this group of patients and inclisiran[8,31,32].

Recommendation	**Class**	**Level**
In primary prevention patients at high and very high cardiovascular risk, who despite optimal, maximally tolerated doses of statins and ezetimbe, are not on the LDL-C target, bempedoic acid may be considered.	**IIb**	**B**

4.1.1. Inflammation in CVD

ASCVD has long been recognised as an inflammatory disease[47], however it is only recently that the therapeutic benefit of anti-inflammatory agents in preventing CVD has been demonstrated[48]. The CANTOS trial demonstrated that canakinumab (a human anti-IL-1β monoclonal antibody) significantly reduced cardiovascular events, without affecting plasma lipids, but unfortunately with significant increase of life-threatening adverse events[49]. Subsequently, colchicine has been demonstrated to reduce CV events and inflammatory markers in individuals with CVD[50]. Based on the available phase-3 trials bempedoic acid was showed to reduce C-reactive protein (CRP) by even 42% (especially in those with already elevated CRP levels ≥2 mg/L)[51]. In the CLEAR Outcomes study at 6 months, the difference in the percent change in the median hsCRP level was −21.6% (95%CI, −23.7 to −19.6) in favor of bempedoic acid[23]. Despite these beneficial results, currently there is still no direct evidence of a clinical benefit of the CRP reduction associated with bempedoic acid. In the animal studies, bempedoic acid mediated the activation of hepatic AMP-activated protein kinase (AMPK), a protein involved in inflammatory signalling, which is associated with the reduction of low-grade inflammation[51,52]. The activation of AMPK may contribute to, observed in phase-3 trials, hsCRP significant lowering with bempedoic acid[51]. We believe the drug may be considered as part of the therapeutic regiment when CRP (or other inflammatory markers) are notably elevated[53].

Recommendation	**Class**	**Level**
Bempedoic acid may be considered in patients at high and very high cardiovascular risk with elevated level of C-reactive protein.	**IIb**	**B**

4.1.2. Type 2 diabetes and metabolic syndrome

As described above, bempedoic acid has beneficial effects on plasma glucose, in contrast with statins which, especially in large doses may increase the risk of new onset diabetes. This effect of statins is small (50-100 new cases of diabetes for every 10,000 patients treated with statins for 5 years), and

the overall effect of statins is overwhelmingly beneficial in these patients (3,5-5x higher benefit in reduction of CVD events risk)[5,8,28]. Nevertheless, a meta-analysis including 2419 patients has demonstrated that bempedoic acid treatment results in a significant reduction in new onset or worsening diabetes (OR 0.66; 95%CI 0.48-0.90)[54]. These results were confirmed in a patient-level (n=3621) pooled analysis of phase 3 RCTs evaluating changes in glycaemia with the results analysed by baseline glycaemic status (diabetes, prediabetes, or normoglycaemia)[55]. They showed that the annual rate of new-onset diabetes for bempedoic acid vs placebo in patients with normoglycaemia at baseline was 0.3% versus 0.8%, and for patients with prediabetes at baseline it was 4.7% versus 5.9%. In patients with diabetes or prediabetes, bempedoic acid significantly ($p<0.0001$) reduced HbA1c by -0.12% and -0.06%, respectively, and did not worsen fasting glucose versus placebo[55]. The results of the CLEAR Outcomes study in fact confirmed these beneficial properties of bempedoic acid, suggesting numerically less patients with new onset diabetes (both in those with prediabetes and diabetes at baseline, and in those with normoglycaemia at baseline) with absolute between-group difference in incidence by 0,8-1% in favour of the bempedoic acid, however without significant risk reduction of new onset diabetes with bempedoic acid (HR 0.95, 0.83 to 1.09)[23].

Nevertheless, these facts may result in bempedoic acid being considered for patients in whom glucose control is a concern. ILEP experts have previously recommended that bempedoic acid and ezetimibe should be added to statin therapy for patients with diabetes who are required to reduce LDL-C by 65–80% from baseline[56].

Recommendation	**Class**	**Level**
Bempedoic acid may be considered in patients at the high and very high cardiovascular risk with prediabetes and diabetes to reduce the risk of new onset diabetes and improve glycaemia.	**IIb**	**B**

Conclusions

Bempedoic acid is safe, well tolerated and results in appreciable reductions in LDL-C, as well as exerting beneficial effects on plasma glucose and inflammatory markers. In light of these beneficial effects, bempedoic has an important role to play in mono- but especially in combination therapy to aid the achievement of lipid goal attainment. Obviously, now the largest challenge is to have bempedoic acid finally available in most countries with good reimbursement criteria (preferably open) to enable its wide application. Further, expecting real-world evidence data will help us to confirm and/or extend its role in the lipid disorders management.

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