Pharmacological Research 231 (2026) 108348

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Targeting ATP-citrate lyase across cardiometabolic and oncologic disease

Chiara Macchi [a,1], Silvia Pedretti [a,b,1], Serena Ghisletti [a,b,*], Alberto Corsini [a], Nico Mitro [a,b], Cesare R. Sirtori [a], Massimiliano Ruscica [a,c,*]

[a] Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", Università degli Studi di Milano, Milan, Italy
[b] Department of Experimental Oncology, European Institute of Oncology IRCCS, Milan, Italy
[c] Department of Cardio-Thoracic-Vascular Diseases, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

ARTICLE INFO

Keywords:
ATP-citrate lyase
Bempedoic acid
Epigenetic regulation
Lipid lowering drugs
Metabolic dysfunction-associated steatotic liver disease
Cancer

ABSTRACT

ATP-citrate lyase (ACLY) is a key metabolic enzyme that links mitochondrial citrate export to the generation of cytosolic acetyl-CoA, thereby supporting *de novo* lipogenesis, cholesterol biosynthesis, protein acetylation, chromatin remodelling, and transcriptional control. Interest in ACLY inhibition initially arose from its lipid-lowering properties and led to the clinical development of bempedoic acid, whose ability to reduce low-density lipoprotein cholesterol and improve cardiovascular outcomes now provides the strongest clinical proof of concept for targeting this pathway. Beyond dyslipidaemia, preclinical evidence suggests that targeting the ACLY pathway and related bempedoic acid-responsive metabolic programs may ameliorate metabolic dysfunction-associated steatotic liver disease (MASLD). ACLY inhibition is expected to reduce *de novo* fatty-acid and cholesterol synthesis by limiting cytosolic acetyl-CoA availability, whereas parent bempedoic acid can directly activate PPARα, and thereby enhance fatty-acid oxidation. However, unlike the cardiovascular setting, robust clinical data supporting ACLY inhibition in MASLD are still lacking. More recently, the identification of nuclear ACLY functions has substantially expanded its biological significance, establishing ACLY as a metabolic–epigenetic integrator that couples nutrient availability to chromatin remodelling, transcriptional programs and immune responses. In cancer, dysregulated ACLY activity contributes to tumour growth, metabolic plasticity, therapy resistance and immune evasion, and its inhibition has shown promising antitumour effects in preclinical models. This review summarizes ACLY biology and pharmacology, emphasizing established cardiovascular applications, emerging MASLD opportunities and exploratory oncologic indications, while highlighting unresolved translational questions.

1. Introduction

Interest in the pharmacological inhibition of ATP-citrate lyase (ACLY), a key enzyme directing extra-mitochondrial carbon flux towards lipid biosynthesis, emerged in the early 2000s [1,2]. During this period, preclinical studies began to show favourable effects on lipid profiles, glucose homeostasis and atherosclerosis progression. The compound initially known as ETC1002 (also termed ESP55016; 8-hydroxy−2,2,14,14-tetramethylpentadecanedioic) is now recognized as bempedoic acid.

A major mechanistic advance occurred in 2016, when Pinkosky et al. established that bempedoic acid was a prodrug requiring activation by very long-chain acyl-CoA synthetase−1 (ACSVL1). Once converted to its CoA derivate, it directly modulates the activity of ACLY and AMP-activated protein kinase (AMPK) [3]. This finding proved clinically relevant because ACSVL1 expression is largely restricted to the liver, thereby confining drug activation predominantly to hepatic tissue. This liver-selective mechanism opened new therapeutic opportunities for individuals experiencing statin-associated muscle symptoms (SAMS), the leading cause of statin discontinuation and an important contributor to atherosclerotic cardiovascular diseases (ASCVD) [4].

These observations led to the CLEAR (Cholesterol Lowering via BEmpedoic Acid, an ACL-inhibiting Regimen) clinical development program, designed to evaluate the long-term safety and effectiveness of bempedoic acid [5]. This effort culminated in the CLEAR Outcomes trial (Evaluation of Major Cardiovascular Events in Participants With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid (ETC−1002) or Placebo), which assessed

* Correspondence to: Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", Università degli Studi di Milano, Via Balzaretti 9, Milan, Italy.
E-mail addresses: serena.ghisletti@unimi.it (S. Ghisletti), massimiliano.ruscica@unimi.it (M. Ruscica).
[1] These authors contributed equally.

https://doi.org/10.1016/j.phrs.2026.108348
Received 10 June 2026; Received in revised form 10 July 2026; Accepted 18 July 2026
Available online 20 July 2026

cardiovascular benefit in statin-intolerant patients [6]. Collectively, these studies supported regulatory approval by both the EMA (European Medicines Agency) and the FDA (Food and Drug Administration) for use as a hypocholesterolaemic agent.

Beyond lipid lowering, the therapeutic potential of ACLY inhibition has expanded into the field of the Metabolic dysfunction-associated steatotic liver disease (MASLD) [7]. Pharmacological ACLY inhibition, along with Mendelian randomization studies of ACLY-modulating human variants, has demonstrated improvements in hepatic stellate cell activation, liver inflammation, and fibrosis in preclinical models and reductions in circulating biomarkers of metabolic dysfunction-associated steatohepatitis (MASH) in humans [8]. These observations have stimulated the development of ACLY-targeted molecules, e.g. enedioic acid inhibitor 326E, which markedly reduces hepatic lipid accumulation and ameliorates MASH in murine models [9]. Moreover, the small-molecule ACLY inhibitor EVT0185 has recently been reported to modulate tumour metabolism, enhance anti-tumour immune responses, and suppress tumour progression in MASH-driven hepatocellular carcinoma (HCC) [10]. More recently, parent bempedoic acid has also been shown to directly bind and robustly induce peroxisome proliferator-activated receptor (PPAR)α signalling and fatty acid oxidation [11].

It is also increasingly evident that ACLY functions beyond the cytoplasm, contributing to nuclear acetyl-CoA pools required for epigenetic regulation, including *de novo* histone acetylation [12].

Given the growing interest in the design and synthesis of new macrocyclic ACLY inhibitors [13], the aim of the present up-to-date narrative review is to provide a critical evaluation of ACLY inhibition across a broad spectrum of clinical contexts, including cholesterol lowering, metabolic liver diseases, and cancer biology.

2. Structure and function of ATP-citrate lyase

ACLY is a magnesium- and ATP-dependent enzyme that catalyses the conversion of citrate and coenzyme A (CoA) into acetyl-CoA and oxaloacetate (OAA) [14]. In humans, ACLY exists as a homotetrameric cytosolic protein composed of four identical polypeptide chains. Each subunit contains 1101 amino acids and has a molecular mass of approximately 120 kDa. The enzyme is highly conserved across species, exhibiting nearly 98% amino acid sequence identity with its rat counterpart [15].

ACLY occupies a pivotal position at the interface of carbohydrate and lipid metabolism by supplying cytosolic acetyl-CoA from mitochondrial citrate. The enzyme catalyses the ATP-driven cleavage of citrate in the presence of CoA and Mg^{2+}, generating acetyl-CoA and oxaloacetate while coupling this thermodynamically unfavourable reaction to ATP hydrolysis [16,17]. During periods of nutrient abundance, particularly when carbohydrate intake is high and lipid demand is low, glycolytic activity increases substantially, producing large amounts of pyruvate in the cytosol. While some pyruvate is converted to lactate, a significant proportion is transported into mitochondria, where the pyruvate dehydrogenase complex converts it into acetyl-CoA.

Because acetyl-CoA cannot traverse the inner mitochondrial membrane, cells employ an indirect transport mechanism to deliver acetyl groups to the cytosol. Within the mitochondrial matrix, acetyl-CoA condenses with oxaloacetate through the action of citrate synthase, forming citrate (Fig. 1). As citrate accumulates, it is exported to the cytoplasm via the tricarboxylate transporter SLC25A1, commonly referred to as the citrate carrier (Fig. 1). Cytosolic citrate then becomes the substrate for ACLY, which regenerates acetyl-CoA and oxaloacetate, thereby effectively transferring mitochondrial acetyl units into the cytosolic compartment (Fig. 1).

The metabolites produced by ACLY support numerous anabolic and

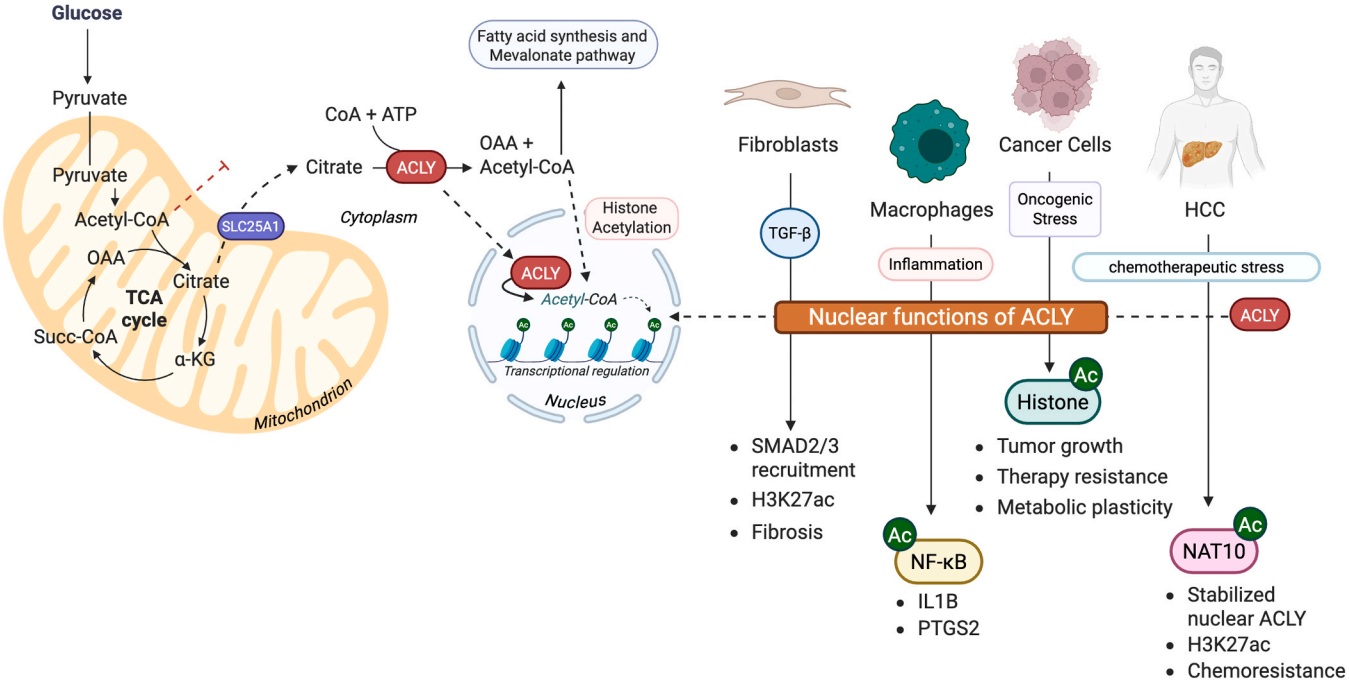

Fig. 1. Cytoplasmic and nuclear ACLY generate acetyl-CoA pools for metabolic and epigenetic functions. In mitochondria, glucose-derived pyruvate is converted into acetyl-CoA, which condenses with oxaloacetate (OAA) to form citrate within the tricarboxylic acid (TCA) cycle. Because acetyl-CoA cannot cross the inner mitochondrial membrane, citrate is exported to the cytoplasm through the mitochondrial citrate carrier SLC25A1. Cytoplasmic ACLY cleaves mitochondria-derived citrate into acetyl-CoA and OAA, generating the cytoplasmic acetyl-CoA pool required for *de novo* fatty acid synthesis, the mevalonate pathway, and protein acetylation. In addition to its cytoplasmic localization, ACLY can translocate to the nucleus, where it locally produces acetyl-CoA to support histone acetylation and transcriptional regulation. ACLY, ATP-citrate lyase; CoA, coenzyme A; H3K27ac, histone H3 lysine 27 acetylation; HCC, hepatocellular carcinoma; IL1B, interleukin 1 beta; KG, ketoglutarate; OAA, oxaloacetate; PTGS2, prostaglandin-endoperoxide synthase 2; SLC25A1, solute carrier family 25 member 1; SMAD2/3, Sma- and Mad-related protein; TGF, transforming growth factor. Created in BioRender. Pedretti, S. (2026) https://BioRender.com/uvucd62.

regulatory pathways. Oxaloacetate may contribute to hepatic glucose production through gluconeogenesis or be reduced to malate and subsequently transported back into mitochondria, where it participates in tricarboxylic acid cycle metabolism. Acetyl-CoA, in contrast, serves as a central metabolic intermediate and donor of acetyl groups for a wide range of biosynthetic processes. One of its principal fates is conversion to malonyl-CoA by acetyl-CoA carboxylase, representing the committed and rate-limiting step of de novo fatty acid synthesis.

In addition to its role in lipogenesis, ACLY-derived acetyl-CoA provides the substrate required for the mevalonate pathway (Fig. 1). This pathway begins with the condensation of two acetyl-CoA molecules to form acetoacetyl-CoA and ultimately gives rise to cholesterol as well as several non-sterol isoprenoid intermediates, including farnesyl pyrophosphate and geranylgeranyl pyrophosphate. These molecules are essential for protein prenylation and the regulation of numerous intracellular signalling pathways.

Furthermore, the acetyl-CoA pools generated by ACLY provide essential substrates for protein acetylation reactions, thereby influencing chromatin structure, gene expression, and intracellular signalling pathways. A major advance in recent years has been the recognition that ACLY is not restricted to the cytosol but can also localize to the nucleus, where it contributes directly to the local production of acetyl-CoA required for histone acetylation and transcriptional regulation [18]. Similar nuclear functions have been described for several other acyl--CoA–producing enzymes, including pyruvate dehydrogenase (PDH), oxoglutarate dehydrogenase (OGDH), and acyl-CoA synthetase short-chain family member 1 and 2 (ACSS1 and ACSS2) [12, 19–26]. These findings have revealed a previously underappreciated link between cellular metabolism and epigenetic regulation, whereby the spatial compartmentalization of acetyl-CoA synthesis enables precise control of chromatin remodelling and gene transcription.

3. Pharmacological landscape of ACLY inhibitors

Although bempedoic acid currently represents the only clinically approved pharmacological strategy targeting ACLY, it should not be considered synonymous with ACLY inhibition as a biological concept. This distinction is particularly important because bempedoic acid has two separable activities: after ACSVL1-dependent conversion to bempedoyl-CoA, it inhibits ACLY and thereby limits cytosolic acetyl-CoA generation for fatty-acid and cholesterol synthesis; parent bempedoic acid can directly activate PPARα and induce fatty-acid oxidation independently of ACLY inhibition. A broader set of ACLY inhibitors has been developed and used as pharmacological tools or investigational compounds (Fig. 2), providing complementary information on ACLY biology, inhibitor binding modes, tissue selectivity, compensatory metabolic pathways, and therapeutic opportunities. Pearce et al. identified SB−201076 as a potent ACLY inhibitor, with a Ki of approximately 1 μM against both rat liver and recombinant human ACLY. However, despite its enzymatic potency, SB−201076 failed to inhibit cholesterol or fatty-acid synthesis in HepG2 cells, indicating poor intracellular access. Its γ-lactone derivative SB−204990 overcame this limitation by acting as a cell-permeable prodrug: although SB−204990 does not directly inhibit ACLY, it entered hepatocytes and was hydrolysed intracellularly to SB−201076, leading to marked inhibition of cholesterol and fatty-acid synthesis. In rats, intravenous SB−204990 also inhibited hepatic cholesterol and fatty-acid synthesis, supporting its value as an early *in vivo* tool to validate ACLY inhibition as a hypolipidemic strategy [27]. Subsequently, Li et al. described a 2-hydroxy-N-arylbenzenesulfonamides class of compounds as ACLY inhibitors that structurally deviate from citrate and demonstrate higher cell permeability and *in vivo* bioavailability. Chronic administration of BMS−303141 in high-fat–fed mice reduced weight gain and lowered plasma cholesterol, triglycerides, and glucose. All these data were consistent with the hypothesis that ACLY might be an attractive target for the treatment of metabolic disorders, including obesity and dyslipidaemia [28]. In C57BLKS/J db/db mice with severe obesity, type 2 diabetes mellitus, and prone to renal injuries, BMS−303141 reduced renal ectopic lipid accumulation, lipogenic enzyme expression, inflammation, and tubulointerstitial fibrosis, supporting the broader relevance of ACLY-dependent lipid flux beyond classical hepatic lipid metabolism [29]. A further advance was the identification of NDI−091143, a low-nanomolar ACLY inhibitor derived from the 2-hydroxy-N-arylbenzenesulfonamide series. NDI−091143 inhibits human ACLY with high affinity, showing an IC_{50} of approximately 2.1 nM, a Ki of 7.0 ± 0.8 nM compared to citrate, and a Kd of 2.2 ± 1.4 nM by surface plasmon resonance. Although kinetic analyses indicated apparent competition with citrate, cryo-electron microscopy of full-length human ACLY in complex with NDI−091143 and ADP revealed that the compound does not occupy the canonical citrate-binding site. Instead, it binds a mostly hydrophobic allosteric cavity within the citrate domain, adjacent to the citrate-binding region. Binding of NDI−091143 stabilizes major conformational rearrangements, including displacement of Arg379, which normally participates in citrate recognition, and movement of Ile344 into the citrate-binding site. Through this mechanism, NDI−091143 indirectly prevents citrate binding and thereby inhibits ACLY catalysis. This discovery not only provided the first structural view of full-length human ACLY in an inhibitor-bound state, but also revealed a previously unrecognized druggable allosteric pocket, offering a rational framework for the design of more potent and selective ACLY inhibitors [30]. EVT0185 is a recently described orally active ACLY-targeting compound with the chemical name

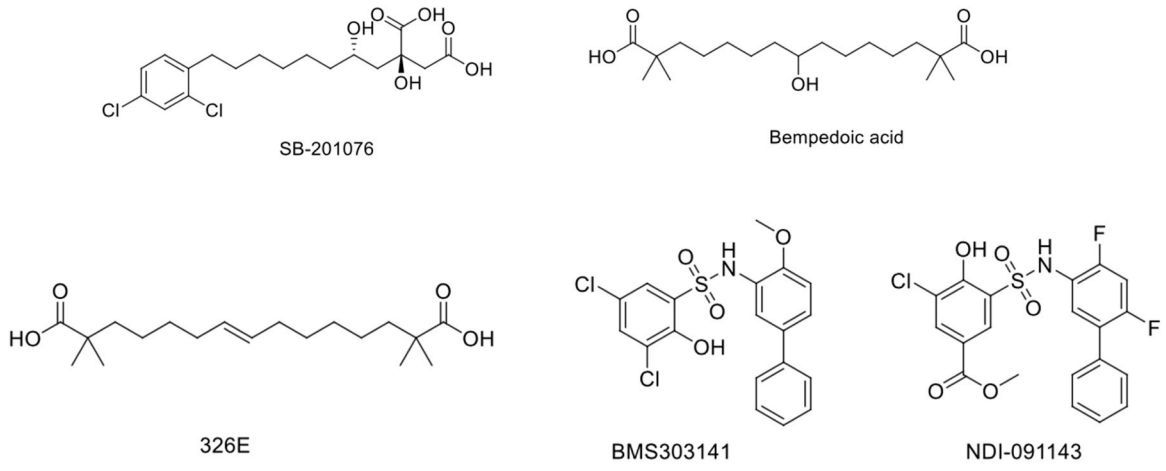

Fig. 2. Structure of ACLY inhibitors. Representative chemotypes of ACLY inhibitors. ACLY, ATP-citrate lyase. Reproduced with permission of Elsevier [35].

6-[4-(5-carboxy−5-methylhexyl)-phenyl]−2,2-dimethylhexanoic acid and molecular formula. Structurally, it belongs to a dicarboxylic acid/decoy fatty-acid-like scaffold, conceptually related to liver-activated ACLY inhibitors such as bempedoic acid but with distinct pharmacology. EVT0185 is converted in the liver by SLC27A2 into its active CoA-thioester metabolite, EVT0185-CoA, which directly interacts with the CoA-binding site of ACLY [10]. 326E is an investigational orally active ACLY inhibitor characterized by an enedioic acid scaffold and selected as the active E-isomer. Similar to bempedoic acid, 326E requires conversion to a CoA-thioester metabolite; 326E-CoA inhibited recombinant human ACLY with an IC_{50} of 5.31 ± 1.21 μmol/L and acted competitively with respect to CoA [31]. Inspired by the structural features of natural ACLY inhibitors, Zhang et al. successfully designed and synthesized a series of novel chalcone derivatives as highly potent and selective ACLY inhibitors [13]. In this context, it should be acknowledged that nucleic acid-based strategies such as Aclysiran have been proposed as potential tools to reduce ACLY activity and improve metabolic phenotypes [32]. Finally, despite ongoing advances in rational drug design, natural products with validated *in vivo* inhibitory effects on ACLY remain scarce. Among the most promising candidates are hydroxycitrate [33] and isoginkgetin [34] as well as compounds containing a hydroxyphenylacryloyl moiety, such as herbacetin and caffeic acid [35].

4. Bempedoic acid and LDL-C lowering through hepatic ACLY inhibition

In line with the scope of this up-to-date review, we summarize the most recent evidence regarding the role of bempedoic acid in cardiovascular prevention. For earlier data from phase 3 clinical trials, readers are referred to previous comprehensive reviews on the topic [36–40].

4.1. Bempedoic acid in current guidelines for hypercholesterolaemia management

Supported by the results of 4 phase 3 studies (CLEAR Harmony, CLEAR Wisdom, CLEAR Tranquility, and CLEAR Serenity) and the cardiovascular outcomes data from the landmark CLEAR OUTCOMES trial [6, 41–43] (Table 1), the most recent European [44] and American [45] guidelines for the management of dyslipidaemia have strengthened their recommendations for the use of bempedoic acid (e.g. Class I, IIa, depending on the clinical setting) as an evidence-based option for patients requiring additional LDL-C reduction or for those who are unable to tolerate statins (Table 2).

4.2. Sub-analyses of the CLEAR outcomes

In a prespecified sub-analysis of the CLEAR Outcomes trial, bempedoic acid treatment was associated with a lower overall incidence of cardiovascular events, including a 20% reduction in MACE−4 (HR 0.80; 95%CI 0.72–0.89), a 17% reduction in MACE−3 (HR 0.83; 95%CI 0.73–0.93), a 31% reduction in myocardial infarction (HR 0.69; 95%CI 0.58–0.83), and a 22% reduction in coronary revascularization (HR 0.78; 95%CI 0.68–0.89). By contrast, no statistically significant effect was observed for stroke [46]. The proportional benefit of bempedoic acid was present in both primary prevention and secondary prevention settings. In the primary prevention cohort, the normalized HR for major vascular events was 0.55, whereas in the secondary prevention cohort it was 0.79; both estimates were broadly consistent with the range of benefit predicted from prior statin meta-analyses. Overall, this study supports the view that bempedoic acid confers cardiovascular risk reduction comparable to statins for an equivalent absolute lowering of LDL-C, reinforcing the principle that the extent of LDL-C reduction is a key determinant of clinical benefit [47].

To determine whether the cardiovascular benefit achieved with bempedoic acid was proportional to LDL-C lowering in a manner comparable to that established for statins by the Cholesterol Treatment Trialists' Collaboration (CTTC), specific CTTC-defined endpoints were chosen. Lincoff et al. found that a first major vascular event occurred in 10.1% of patients treated with bempedoic acid compared to 11.7% of those receiving placebo, corresponding to a HR of 0.85. At 12 months, bempedoic acid produced a placebo-corrected LDL-C reduction of 22.4 mg/dL. When the treatment effect was normalized to a 1 mmol/L LDL-C reduction, the HR for major vascular events was 0.75, which was very similar to the 0.78 rate ratio previously reported for statins in the CTTC meta-analysis. Comparable normalized benefits were also observed for major coronary events, nonfatal myocardial infarction, and coronary revascularization, supporting the concept that the clinical benefit of bempedoic acid is largely explained by the magnitude of LDL-C lowering rather than by a drug-specific mechanism distinct from that

Table 1
Main results of phase 3 CLEAR trials.

Study	Duration	Population	Results
CLEAR Wisdom	**52 weeks**	Patients with ASCVD and/or HeFH and LDL -C> 70 mg/dL while receiving maximally tolerated statin (with or without other LLT)	At 12 weeks: Bempedoic acid added to maximally tolerated statin (with or without other LLT) reduced LDL-C by 17.4% (95% CI, −21.0,−13.9) more than placebo (P < .001)
CLEAR Harmony	**52 weeks**		At 12 weeks: Bempedoic acid added to different intensities of background statin treatment (low, moderate, or high) with or without additional LLT reduced LDL-C from baseline (difference vs placebo. – 18.1% (95%CI, −20.0%, - 16.1%): P < .001
CLEAR Tranquility	**12 weeks**	Patients with hypercholesterolemia and a history of statin intolerance who required additional LDL-C lowering	At 12 weeks: Bempedoic acid added to stable LLT, including ezetimibe, reduces LDL-C up to 28.5% (95%CI, −34.4, −22.5) more than placebo (P < .001)
CLEAR Serenity	**24 weeks**		At 12 weeks: Treatment with bempedoic acid reduced LDL-C 21.4% (95%CI, −25.1, −17.7) more than placebo (P < .001)
CLEAR Outcomes	**median of 40.6 months**	- Randomised, double-blind, placebo-controlled trial of 13,970 statin-intolerant adults with established ASCVD or at high risk for ASCVD - Fasting blood LDL-C ≥ 100 at screening	The primary endpoint was MACE−4 (nonfatal MI, nonfatal stroke, coronary revascularization, or CV death): 11.7% (for bempedoic acid) vs. 13.3% (placebo), HR 0.87, 95%CI 0.79–0.96 (p = 0.004). Absolute risk reduction ~1.6%. LDL-C lowering was ~21% vs near-zero in placebo at 6 months.

CLEAR Wisdom, Evaluation of Long-Term Efficacy of Bempedoic Acid (ETC−1002) in Patients With Hyperlipidemia at High Cardiovascular Risk; CLEAR Harmony, Evaluation of Long-Term Safety and Tolerability of ETC−1002 in High-Risk Patients With Hyperlipidemia and High CV Risk; CLEAR Tranquility, Evaluation of the Efficacy and Safety of Bempedoic Acid (ETC−1002) as Add-on to Ezetimibe Therapy in Patients With Elevated LDL-C; CLEAR Serenity, Evaluation of the Efficacy and Safety of Bempedoic Acid (ETC−1002) in Patients With Hyperlipidemia and Statin Intolerant; CLEAR OUTCOME, Evaluation of Major Cardiovascular Events in Participants With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid (ETC−1002) or Placebo.
ASCVD, atherosclerotic cardiovascular disease; HeFH, Heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy.

Table 2
Recommendation use of bempedoic acid according to European and American Guidelines.

2025 EAS/ESC update		
Clinical Scenario	**Recommendation**	**Key use**
Primary or Secondary Prevention	Class I, Level A	Non-statin therapies with proven cardiovascular benefit (including bempedoic acid), taken alone or in combination, are recommended for patients who are unable to take statin therapy to lower LDL-C levels and reduce the risk of CV events. The choice should be based on the magnitude of additional LDL-C lowering needed
Primary or Secondary Prevention	Class I, Level B	Bempedoic acid is recommended in patients who cannot take statin therapy to achieve the LDL-C goal
Primary or Secondary Prevention	Class IIa, Level C	As an add-on therapy to maximally tolerated statin therapy with or without ezetimibe in patients at high or very high CV risk who do not achieve LDL-C goal
2026 AHA/ACC		
Primary prevention	**Recommendation**	**Key use**
LDL-C Levels 70–189 mg/dL	Class 2, Level B-NR	In adults at high (≥10%) 10-year estimated risk for ASCVD on maximally tolerated statin with or without ezetimibe, if a goal LDL-C < 70 mg/dL is not achieved
Severe Hypercholesterolemia Without HeFH	Class 1, Level B-NR	In adults with severe hypercholesterolemia with an LDL-C ≥ 190 mg/dL without clinical ASCVD but with clinical or genetic confirmation of HeFH to achieve a goal of LDL-C < 100 mg/dL
Severe Hypercholesterolemia With HeFH	Class 1, Level B-R	In adults with severe hypercholesterolemia with an LDL-C ≥ 190 mg/dL without clinical ASCVD but with clinical or genetic confirmation of HeFH to achieve a goal of LDL-C < 70 mg/dL
Severe Hypercholesterolemia With Clinical ASCVD	Class 1, Level B-R	In adults with severe hypercholesterolemia with an LDL-C ≥ 190 mg/dL and clinical ASCVD who are on maximally tolerated statin therapy to achieve a goal of LDL-C < 55 mg/dL
HoFH	Class 2a, Level B-R	In adults with clinical or genetic confirmation of HoFH the addition is reasonable to lower LDL-C
Adults With Diabetes Without Established ASCVD	Class 1, Level B-R	In adults with diabetes who have statin-attributed side effects is recommended to lower LDL-C.
Secondary prevention	**Recommendation**	**Key use**
In adults with clinical ASCVD who are not at very high risk	Class 2a, Level B-R	Already on maximally tolerated statin therapy to achieve a goal of LDL-C < 70 mg/dL
In adults with clinical ASCVD who are at very high risk	Class 2a, Level B-R	Already on maximally tolerated statin therapy to achieve a goal of LDL-C < 55 mg/dL
Adults With Subclinical Coronary Atherosclerosis (CAC score of ≥300)	Class 2a, Level B-NR	To achieve a goal of LDL-C < 55 mg/dL

ASCVD, Atherosclerotic Cardiovascular Disease; CAC, Coronary Artery Calcium; CV, Cardiovascular; HeFH, Heterozygous Familial Hypercholesterolemia; HoFH, Homozygous Familial Hypercholesterolemia; LDL-C, Low-density lipoprotein cholesterol.
Class I, the treatment/procedure is recommended/indicated; Class IIa, it should be considered; Class 1 (strong recommendation), The benefit clearly outweighs the risk, so the intervention/procedure should be performed or given in most patients under most circumstances; Class 2a (moderate recommendation), The benefit is probably greater than the risk, so the intervention/procedure is reasonable and should be considered; Level A, evidence from multiple randomized clinical trials or meta-analyses; Level B, evidence from a single randomized clinical trial or large non-randomized studies; Level C, evidence from expert consensus, small studies, retrospective studies, or registries; Level B-R, evidence comes from moderate-quality randomized data — typically one or more randomized trials, or meta-analyses of moderate-quality randomized studies; Level B-NR, evidence comes from moderate-quality nonrandomized data — for example well-designed observational studies, registries, or other nonrandomized analyses.

of statins [47].

Among individuals at high ASCVD risk, those with diabetes mellitus remain at higher risk although diabetes mellitus–related excess mortality is lower in the contemporary era than previously [48]. During a median follow-up of 3.4 years, bempedoic acid was associated with significant relative and absolute reductions in MACE−4 risk among patients with diabetes compared with placebo (absolute risk reduction 2.4%), without evidence of differential treatment effect across glycaemic strata. The occurrence of new-onset diabetes did not differ significantly between groups (HR 0.95; 95%CI, 0.83–1.09). Likewise, in individuals with prediabetes or normoglycaemia, HbA1c concentrations at month 12 and at the end of the study remained comparable between randomized groups. Notably, LDL cholesterol and high-sensitivity C-reactive protein levels at 6 months were significantly reduced with bempedoic acid vs placebo across all glycaemic strata (diabetes, prediabetes, and normoglycaemia) [49]. In this context, Federici et al. provided an Italian diabetologist-led expert opinion on the role of bempedoic acid in the management of dyslipidaemia in people with diabetes, positioning it as an oral lipid-lowering option particularly relevant for patients with residual hypercholesterolaemia despite statin/ezetimibe therapy or with partial/complete statin intolerance. They propose practical treatment algorithms, in which bempedoic acid can help to reduce residual cardiovascular risk and bridge treatment gaps in patients who may not be eligible for or have access to PCSK9 inhibitors, thus representing a valuable addition to personalised lipid management strategies aimed at lowering cardiovascular morbidity and mortality in this high-risk population [50].

Another enhancing ASCVD comorbidity is obesity. Bempedoic acid showed clinically meaningful efficacy in statin-intolerant patients with obesity (BMI ≥30 kg/m^2), reducing LDL-C by 22.5% and hs-CRP by 23.2% at 6 months, while also lowering the risk of MACE−4 by 23% over a median follow-up of 40.7 months. Significant reductions were also observed for myocardial infarction, coronary revascularization, and stroke, whereas cardiovascular and all-cause mortality were not significantly affected. The drug was generally well tolerated and did not worsen HbA1c or increase new-onset diabetes, although higher rates of hyperuricemia/gout and some laboratory abnormalities were observed [51]. Although these findings rely mostly on White and statin-intolerant population, these data may be particularly relevant in obesity, a condition characterized by both atherogenic dyslipidaemia and systemic inflammation, suggesting that the dual reduction in LDL-C and hs-CRP

may be mechanistically and clinically important [52]. It could be speculated that such inflammatory effects should not automatically be ascribed to ACLY inhibition alone, because PPARα activation by parent bempedoic acid may also contribute to lipid oxidation and inflammatory modulation, although its quantitative contribution in clinical settings remains undefined [11]. According to this finding, bempedoic acid could act beyond hepatocytes and stimulate PPARα activity in all cell types where PPARα is present, such as macrophages, renal cells, and cardiomyocytes.

Relative to the residual inflammatory risk, a CLEAR Outcomes study showed that at 6 months, treatment with bempedoic acid led to a 21.6% reduction in median hs-CRP and a 21.1% reduction in mean LDL-C compared with placebo. Baseline hs-CRP was significantly associated with future risk, with patients in the highest quartile showing a greater likelihood of experiencing the primary composite cardiovascular endpoint (HR 1.43; 95%CI 1.24–1.65), cardiovascular death (HR 2.00; 95%CI 1.53–2.61), and all-cause death (HR 2.21; 95%CI 1.79–2.73) than those in the lowest quartile. By comparison, the predictive value of baseline LDL-C was weaker for the primary composite endpoint (HR 1.19; 95%CI 1.04–1.37) and absent for cardiovascular mortality (HR 0.90; 95%CI 0.70–1.17) and all-cause mortality (HR 0.95; 95%CI 0.78–1.16). Elevated hs-CRP identified high-risk individuals irrespective of baseline LDL-C, while the cardiovascular benefit of bempedoic acid remained consistent across all levels of both biomarkers [43]. The hs-CRP-lowering effect of bempedoic acid was further corroborated by a meta-analysis of phase II-IV randomized, parallel-group trials in adults (≥18 years) comparing bempedoic acid, at any dose, with placebo or an active comparator. Across studies, bempedoic acid consistently reduced hs-CRP levels. The absence of significant modification by ezetimibe co-administration suggests that this anti-inflammatory effect is mainly attributable to bempedoic acid itself. Nevertheless, because the analyses were performed at the study level and did not directly account for achieved LDL-C reduction, a causal effect independent of LDL-C lowering cannot be definitively established [53].

Considering that obesity and diabetes are closely linked to MASLD [54], in the CLEAR Outcomes trial it was evaluated whether non-invasive markers of MASLD identify statin-intolerant patients at higher cardiovascular risk and whether they modify the effect of bempedoic acid. Higher baseline scores for liver steatosis, assessed by the Framingham Steatosis Index (FSI), the Fibrosis−4 index (FIB−4) and the NAFLD fibrosis score (NFS), were associated with a greater risk of MACE−4 in the placebo group, with HRs of 1.13 (95%CI 1.08–1.18), 1.21 (95%CI 1.09–1.34), and 1.16 (95%CI 1.10–1.23), respectively, for each 1-unit increase in score, respectively, FSI, FIB−4 and NFS. These findings confirm the close relationship between MASLD-related phenotypes and cardiovascular risk. Bempedoic acid reduced MACE−4 overall, but the largest relative benefit was observed in patients with higher steatosis scores: when FSI was analysed as a continuous variable, the HR for MACE−4 per 1-unit increase in FSI was 1.04 (95%CI 0.99–1.09) in the bempedoic acid group vs 1.14 (95%CI 1.09–1.18) in the placebo group, and in the highest FSI quartile the HR for bempedoic acid vs placebo was 0.70 (95%CI 0.59–0.84). Conversely, fibrosis burden (as assessed by FIB−4 and NFS) did not influence treatment effect. These findings suggest that simple liver-related non-invasive tests may help enrich cardiovascular risk assessment in high-risk dysmetabolic patients and may identify a subgroup with enhanced benefit from bempedoic acid, although the post hoc design and absence of imaging or histological confirmation warrant cautious interpretation [55].

In the context of obesity, the venous thromboembolism (VTE) cannot be overlooked. During CLEAR Outcomes follow-up, 106 VTE events were recorded, including 39 events in the bempedoic acid group and 67 in the placebo group, corresponding to a significant reduction in first VTE occurrence with active treatment (HR 0.58, 95%CI 0.39–0.86). This benefit was consistent across both components of the composite endpoint, with lower rates of deep vein thrombosis (HR 0.56, 95%CI 0.31–0.996) and pulmonary embolism (HR 0.61, 95%CI 0.37–0.996) in patients receiving bempedoic acid. Sensitivity analyses censoring VTE events occurring after a first major adverse cardiovascular event yielded similar findings, supporting the robustness of the association. However, given the *post hoc* design, the limited number of VTE events, and the fact that outcomes were investigator-reported rather than centrally adjudicated, these results should be interpreted as hypothesis-generating. Furthermore, the biological basis linking lipid-lowering therapies to lower thromboembolic risk remains incompletely understood. Possible explanations are extrapolated from pathways shared with statins, including attenuation of systemic inflammation, or upregulation of hepatic LDLRs. The latter mechanism is of particular interest, because increased LDLR expression has been associated in experimental models with enhanced factor VIII clearance, which may contribute to a less prothrombotic milieu. However, since these hypotheses should be considered biologically plausible but still mechanistically unresolved [56].

4.3. Long-term safety and efficacy

Relative to safety, in a *post hoc* analysis of the CLEAR Outcomes trial, Ray et al. evaluated whether uric acid (UA)-lowering therapies influenced gout frequency in statin-intolerant patients receiving bempedoic acid and whether a prior history of gout modified cardiovascular benefit. In the CLEAR Outcomes trial, bempedoic acid was associated with a mean increase in serum UA of approximately 0.8 mg/dL and a higher incidence of gout adverse events than placebo (3.1% vs 2.1%). This analysis showed that gout was infrequent in patients without prior gout and with normal baseline UA (<1% in both groups), whereas risk was higher in those with elevated baseline UA and/or prior gout, especially when both were present. The use of UA-lowering therapy, mostly allopurinol, was associated with a lower frequency of gout across higher-risk subgroups, suggesting that clinically indicated monitoring and treatment of hyperuricemia may mitigate this adverse effect. The cardiovascular benefit of bempedoic acid was similar in patients with and without prior gout (HR 0.87; 95%CI 0.63–1.21) and 0.87 (95%CI 0.79–0.96), respectively), indicating that gout history does not appear to diminish treatment efficacy [57]. This analysis provides practical reassurance that the gout risk associated with bempedoic acid is concentrated in predisposed patients and may be manageable in clinical practice.

Bempedoic acid suggests a small but relevant increase in gallstone incidence [58], raising concerns about its safety in individuals predisposed to biliary disease. The association is biologically plausible because bempedoic acid may shift bile composition toward a more lithogenic state by acting at multiple levels of cholesterol and bile acid homeostasis rather than through a single isolated pathway. Specifically, experimental evidence suggests that bempedoic acid may increase hepatic cholesterol efflux into bile through upregulation of ABCG5/ABCG8, while at the same time reducing bile acid synthesis via suppression of CYP7A1, effects that together could favour cholesterol supersaturation of bile. Additional proposed mechanisms include inhibition of OATP1B1/OATP1B3-mediated bile acid transport, possible interference with MRP1/glutathione handling, enhanced FXR transcriptional activity, and suppression of PXR signalling, all of which may further disturb bile acid recirculation, biliary flow, and gallbladder physiology [59]. The use of bempedoic acid may deserve greater caution in patients already at risk for gallstones, including older adults, women, individuals with obesity, diabetes, rapid weight loss, bariatric surgery, or concomitant exposure to other potentially lithogenic treatments such as fibrates or possibly GLP−1 receptor agonists [59,60]. Overall, its potential impact on bile composition and cholesterol crystallization warrants closer study and may justify individualized risk assessment in susceptible patients.

In the context of safety, it should be also highlighted that it has been shown that bempedoic acid does not impact on mitochondrial functionality and structural organization within skeletal muscle fibres in

apoE$^{-/-}$ mice. In particular, transmission electron microscopy analysis of muscle fibres of tibialis anterior showed that bempedoic acid did not affect the morphology and distribution of mitochondria and mitochondrial functionality of skeletal muscles in mice receiving bempedoic acid was not reduced compared to control group [61].

In the prospective, pragmatic, multicenter CLEAR Taiwan phase 4 study, 180 Taiwanese patients with inadequately controlled hypercholesterolemia or mixed dyslipidemia received bempedoic acid (180 mg/die) in addition to background lipid-lowering therapy, with 160 patients (88.9%) completing 12 weeks of follow-up. The cohort was characterized by a mean age of 61.4 ± 10.4 years, 62.8% male sex, a high burden of established disease (67.2% in secondary prevention), and a substantial prevalence of statin intolerance (46.1%). Bempedoic acid induced a significant median 19% reduction in LDL-C, from 117.5 to 92 mg/dL at week 12, together with significant decreases in non–HDL-C (−13.3%), total cholesterol (−10.8%), apolipoprotein B (−11.5%), and hs-CRP (−34.0%), with minimal and not statistically significant changes in triglycerides, HDL-C, and lipoprotein(a). The magnitude of LDL-C lowering was comparable to that reported in phase 3 trials conducted predominantly in Western populations, thereby extending the generalizability of bempedoic acid lipid-lowering efficacy across ethnic groups. LDL-C target attainment improved meaningfully, with 1/3 of the overall population reaching Taiwanese guideline-recommended goals [62,63]. Specifically, among patients with pre-existing ASCVD, 24.3% achieved LDL-C < 70 mg/dL and 11.2% achieved LDL-C < 55 mg/dL. The marked reduction in hs-CRP compared with that observed in Western studies, may reflect multiple factors, including differences in baseline inflammatory status, genetic background, dietary patterns, cardiometabolic risk profile, as well as the smaller sample size and consequent variability of the estimate. Treatment was generally well tolerated, with no serious adverse events reported; adverse events were mostly mild, treatment discontinuation occurred in 3.3%, and myalgia was uncommon (1.7%), supporting the favourable tolerability profile of bempedoic acid in this real-world Asian setting [64].

This evidence was also confirmed in the Japanese CLEAR-J LONG open-label phase 3 extension study, involving 130 patients with hypercholesterolemia receiving bempedoic acid 180 mg/day for 52 weeks to confirm long-term efficacy and safety after the 12-week confirmatory CLEAR-J trial. LDL-C was reduced by 21.6% overall and by 25.3% in newly enrolled patients, with effects evident from week 4 and maintained through week 52; 65.6% of patients achieved guideline-based LDL-C targets at one year [65]. Long-term reductions were also observed for non–HDL-C (−19.4%), total cholesterol (−16.1%), apoB (−17.0%), and hsCRP (−14.4%), while HbA1c remained essentially unchanged. Bempedoic acid was generally well tolerated with discontinuation due to AEs in 4.6%, and hyperuricemia in 6.2% as the main treatment-related event. Overall, this study confirmed in Japanese patients the durable lipid-lowering efficacy and acceptable long-term safety profile of bempedoic acid, with no new population-specific safety signals [66].

4.4. Real-life data

In a retrospective real-world study from a Milan lipid clinic, 126 patients with high residual cardiovascular risk, with statin intolerance, or familial hypercholesterolemia, and frequent background use of ezetimibe, statins, and PCSK9-targeting therapies showed that bempedoic acid significantly reduced LDL-C from 116.1 ± 49.3 to 78.5 ± 36.0 mg/dL, corresponding to a median relative reduction of −26.1% and an absolute decrease of −32.3 ± 37.1 mg/dL; non–HDL-C and total cholesterol also declined, respectively by −27% and 21%, whereas triglycerides remained unchanged and HDL-C showed only a modest transient decrease (−7.7%). Overall, 60.8% of patients achieved their ESC/EAS LDL-C targets at the last follow-up. LDL-C lowering was attenuated in FH patients (−18% vs −29.2% in non-FH), and FH independently predicted failure to reach target (OR 0.045, 95%CI 0.004–0.523). The magnitude of LDL-C reduction was broadly consistent with prior randomized and real-world studies, while also underscoring the marked interindividual variability in response, potentially related to phenotype, concomitant therapy, and genetic factors. Bempedoic acid was generally well tolerated, with hyperuricemia in 4%, myalgia in 4%, rare mild gastrointestinal events, and treatment discontinuation in 9.5% [67].

In the real-world BEYOND-REAL study, a retrospective cohort of adults (mostly White and not Hispanic or Latino) receiving moderate-intensity statins, bempedoic acid was compared with ezetimibe after 1:1 propensity matching (3353 patients per group). Bempedoic acid was associated with a significantly lower risk of the composite cardiovascular outcome (16.7% vs 22.8%; RR 0.73, 95%CI 0.63–0.84), with consistent benefit across stroke, myocardial infarction, ischemic heart disease, new-onset heart failure, and peripheral artery disease. LDL-C reduction, from baseline, was greater with ezetimibe (−30.9 mg/dL vs −23.5 mg/dL), whereas cardiovascular outcomes still favoured bempedoic acid. This apparent discordance may reflect pleiotropic effects of bempedoic acid, including possible anti-inflammatory actions, although hsCRP and apoB could not be reliably assessed in this database [68].

Evidence for the beneficial effect of bempedoic acid in this setting comes from a Monte Carlo simulation based on the SANTORINI cohort, which modelled stepwise oral lipid-lowering intensification in high- and very-high-risk patients. In this analysis, adding bempedoic acid after statin optimization and ezetimibe further reduced mean LDL-C to 59.8 mg/dL and increased LDL-C goal attainment from 39.1% to 61.8% [69]. By using the same setting within the ITACARE-P (Italian Alliance for Cardiovascular Rehabilitation and Prevention) registry of ASCVD patients not at LDL-C goal, we found that adding bempedoic acid after statin and/or ezetimibe therapy increased overall LDL-C goal attainment from 50% to 63% [70]. Overall, this evidence suggests that bempedoic acid may represent an effective oral intensification strategy, with potential additional benefits in terms of adherence when incorporated into a single-pill combination regimen.

4.5. New clinical trials

In the multicenter, pragmatic, randomized ES-BempedACS trial, 206 patients hospitalized for acute coronary syndrome (ACS) were randomized within 72 h of admission to receive either triple lipid-lowering therapy (high-intensity statin + ezetimibe + bempedoic acid) or dual therapy (high-intensity statin + ezetimibe) for 8 weeks. The study population was relatively young (59.5 ± 10.9 years), predominantly male, and had a mean baseline LDL-C of 133.6 ± 28.8 mg/dL; importantly, 67.0% of patients were statin-naive at presentation. The primary endpoint, namely the proportion of patients achieving LDL-C < 55 mg/dL at 8 weeks, was not significantly different between groups: 59.4% in the triple-therapy arm versus 53.1% in the dual-therapy arm. Likewise, the percentage reduction in LDL-C was almost identical in the two groups, amounting to 57.5 ± 17.8% with triple therapy and 56.9 ± 18.5% with dual therapy, with mean LDL-C values at 8 weeks of 54.6 mg/dL and 55.3 mg/dL, respectively. Target attainment for secondary lipid goals was also high and similar in both groups, with 71.9% vs 73.5% achieving non-HDL-C < 85 mg/dL and 84.4% vs 86.7% achieving triglycerides < 150 mg/dL in the triple- and dual-therapy groups, respectively. The neutral effect of adding bempedoic acid was consistent across sex, age, diabetes status, prior statin exposure, baseline LDL-C, ACS type, and participation in cardiac rehabilitation. Cardiovascular events were infrequent during the short follow-up and did not differ significantly between groups, with events occurring in 4.2% of the triple-therapy arm and 2% of the dual-therapy arm. From a safety perspective, the addition of bempedoic acid was well tolerated, with no significant excess of adverse events; only one patient discontinued treatment because of gout, while hyperuricemia occurred in 7.3% of the triple-therapy group and 5.1% of the dual-therapy group [71]. The lack of incremental efficacy of bempedoic acid seems in line with

dose–response models indicating that the LDL-C–lowering effect of bempedoic acid is attenuated as statin intensity increases [72]. Accordingly, this trial suggests that in the early post-ACS setting, an upfront oral strategy based on high-intensity statin plus ezetimibe may already achieve substantial early lipid control in more than half of patients, whereas the routine addition of bempedoic acid does not appear to confer further short-term lipid benefit, although it appears safe. However, the small patient population, the short follow-up period, and the lack of accurate monitoring of medication adherence limit the strength of these findings, thereby warranting further investigation. A Phase 2 trial for bempedoic acid has recently been completed in children with heterozygous familial hypercholesterolemia (HeFH) aged 6–17 years (NCT05694260). According to an EAS 2026 abstract presentation, Bempedoic acid, when given as a tablet in addition to patient's existing lipid lowering treatments, reduced LDL-C in pediatric patients (range 6–25%) and did not raise any new safety concerns.

Overall, a definitive answer is expected from the The triPle Oral thERapy With Bempedoic Acid vs uSual Care in Early Lipid Management of Patients With acUte coronAry syndrome (PERSUADE; NCT07440381) trial, which will evaluate the effect of triple lipid-lowering therapy—consisting of bempedoic acid, a high-intensity statin, and ezetimibe—initiated during hospitalization for ACS in a larger population of approximately 600 patients. The primary endpoint of the PERSUADE trial is the difference in the mean percentage change in LDL-C levels from baseline to week 8 between the triple-combination therapy group and the usual-care group.

5. Impact of ACLY inhibition and PPARα activation on liver fat

The idea that ACLY inhibition may reduce hepatic fat accumulation by modulating *de novo* lipogenesis dates back to 2022, when Morrow et al. developed a translational mouse model of metabolic dysfunction-associated steatohepatitis (MASH) showing that hepatocyte-specific ACLY inhibition enhanced fatty acid oxidation while decreasing gluconeogenesis, as well as serum and hepatic lipid levels [8]. The study demonstrated that genetic suppression of ACLY in hepatocytes lowers fatty acid and cholesterol synthesis, promotes fatty acid oxidation, and improves glucose intolerance, hepatic steatosis, and hepatocellular ballooning, without elevating circulating triglycerides. Notably, pharmacological inhibition of ACLY with bempedoic acid reproduced the effects observed with genetic inhibition and additionally reduced fibrosis. Follow-up studies in primary mouse and human stellate cells further showed that bempedoic acid enhances fatty acid oxidation and inhibits lipid synthesis in these cells, an effect associated with diminished activation and proliferation. Importantly, Mendelian randomization analyses of *Acly* genetic variants in the UK Biobank suggested that reduced *Acly* activity is linked to lower circulating triglycerides and decreased serum biomarkers associated with MASLD. Altogether, these findings indicated that ACLY inhibition could represent a promising strategy for mitigating MASH, while also exerting beneficial effects on glycaemic control and dyslipidaemia [8].

However, whether targeting *de novo* lipogenesis (DNL) was a viable strategy for MASLD was subject of much investigation, e.g. ACLY deficiency led to seemingly paradoxical increase in liver DNL on high-fat diet with increasing expression of nuclear sterol regulatory element-binding protein 1c and of its target DNL enzymes [73].

Trying to answer this question, Liu et al. aimed to determine whether the beneficial effects of bempedoic acid on liver fat were truly mediated through ACLY inhibition and to clarify how ACLY interacts with compensatory pathways of acetyl-CoA production, particularly acetyl-CoA synthetase (ACSS2), under different nutritional conditions. The conclusions were that the beneficial effects of bempedoic acid on hepatic steatosis were mediated predominantly through ACLY-independent mechanisms, likely involving stimulation of fatty acid oxidation and PPARα-related pathways rather than simple suppression of lipogenic acetyl-CoA generation. By using liver-specific genetic deletion models, hepatic ACLY deficiency unexpectedly exacerbated, rather than alleviated, Western diet-induced steatosis. Compared with controls, mice lacking hepatic ACLY displayed increased liver weight, greater histological steatosis, and higher hepatic levels of triglycerides, diacylglycerols, and cholesterol esters. Mechanistically, the absence of ACLY was associated with suppression of a PPARα-dependent fatty acid oxidation program, including lower expression of canonical oxidative genes, reduced abundance of endogenous PPARα ligand species such as phosphatidylcholine 16:0/18:1, lower short-chain acylcarnitines, reduced ketone production, and impaired fatty acid oxidation. However, the use of bempedoic acid retained a clear anti-steatotic effect despite the absence of hepatic ACLY. In Western diet-fed mice, bempedoic acid markedly reduced liver lipid accumulation in both wild-type and liver-specific ACLY knockout animals, lowering hepatic triglycerides and diacylglycerols, restoring phosphatidylcholine abundance, including PC 16:0/18:1, and increasing expression of PPARα target genes. In parallel, bempedoic acid promoted fatty acid oxidation, as reflected by increased acetylcarnitine and β-hydroxybutyrate production, thus producing a metabolic phenotype that was essentially opposite to that caused by ACLY deficiency itself [74].

Following the same experimental paradigm, Di Pastena et al. provided evidence that the hepatic effects of targeting ACLY cannot be understood by considering ACLY in isolation. The authors investigated EVT0185, a dual inhibitor of ACLY and ACSS2, in several complementary mouse models of MASH and fibrosis, including diet-induced, thermoneutral, FAT-MASH, and CCl4-based models. Across these systems, EVT0185 consistently improved insulin sensitivity, reduced hepatic steatosis, lowered liver and circulating triglycerides and cholesterol, and attenuated histological features of MASH, including ballooning, inflammation, and fibrosis. Notably, antifibrotic effects were also observed in a fibrosis model lacking steatosis, indicating that the compound was acting not only through changes in hepatocyte lipid metabolism but also through direct effects on hepatic stellate cells. The main conceptual advance of this study lies in the demonstration that acetate metabolism through ACSS2 is a major compensatory and profibrotic pathway when ACLY-dependent acetyl-CoA production is limited. EVT0185 suppresses stellate cell activation and collagen production by inhibiting acetate-driven cholesterol synthesis, with this effect requiring SLC27A2-mediated drug activation. Mechanistically, the antifibrotic response appeared to depend more on suppression of sterol biosynthesis than on inhibition of fatty acid synthesis *per se*, because mevalonolactone supplementation reversed the inhibitory effect of EVT0185 on stellate cell activation and proliferation. For the topic of the present review focused on bempedoic acid, the relevance of this paper is twofold. First, it reinforces the idea that single-pathway inhibition of ACLY is unlikely to fully explain improvements in steatosis, because acetate/ACSS2-dependent carbon flux can maintain acetyl-CoA availability and sustain lipogenic and fibrogenic programs. Second, the authors explicitly place their work in the context of prior data showing that bempedoic acid can suppress diet-induced hepatic steatosis independently of hepatocyte ACLY activity, thereby supporting the broader concept that bempedoic acid must exert additional metabolic actions beyond canonical ACLY inhibition [75].

A pivotal conceptual advance for understanding how bempedoic acid may influence hepatic steatosis beyond its canonical inhibition of ACLY came from Papa et al. [11]. The rationale for the study arose from the observation that the established model of bempedoic acid action does not fully explain all its reported metabolic effects. Prior findings showing that bempedoic acid reduced hepatic lipid accumulation even in liver-specific *Acly* knockout mice suggested that additional mechanisms may contribute to its anti-steatotic activity. Moreover, previous experimental evidence had linked bempedoic acid to improvements in hepatic steatosis, inflammation, and fibrosis, while indirect data had suggested possible interactions with AMPK- and PPARα-related pathways, although direct proof was lacking. Against this background, the authors investigated whether bempedoic acid could directly regulate

hepatic lipid metabolism through PPARα. In primary mouse hepatocytes and mouse liver, bempedoic acid robustly upregulated PPAR signalling and fatty acid degradation pathways, together with canonical PPARα target genes involved in lipid oxidation, including *Acaa1b, Acot2, Cyp4a10, Cyp4a14, Ehhadh,* and *Hmgcs2*. These molecular changes were accompanied by increased fatty acid oxidation in hepatocytes, to an extent comparable with that observed using the established PPARα agonist GW7647, while *Ppara* knockdown largely abolished this response. The authors showed that bempedoic acid physically engages the ligand-binding domain of PPARα and stabilizes its active conformation. From the perspective of steatosis, the most relevant aspect of this study is that activation of the PPARα transcriptional network occurred independently of ACSVL1/SLC27A2, indicating that bempedoic acid does not require conversion to bempedoyl-CoA to stimulate this oxidative pathway. This observation supports the view that the hepatic lipid-lowering effect of bempedoic acid may rely not only on reduced lipogenesis through ACLY inhibition, but also on a parallel increase in fatty acid disposal mediated by direct PPARα activation. This mechanism may help explain the broader metabolic effects previously attributed to bempedoic acid, including reductions in liver lipid accumulation, inflammation, and fibrosis, and may potentially extend beyond hepatocytes to other PPARα-expressing tissues. However, the study remains primarily mechanistic, and the relative contribution of PPARα activation versus ACLY inhibition to the anti-steatotic effect of bempedoic acid *in vivo* has not yet been defined [11]. Finally, in this context, the role of lipid droplets in MASLD pathogenesis should not be underestimated. In an acute choline-deficient, L-amino acid-defined, high-fat diet mouse model, bempedoic acid attenuated the liver injury induced by CGI−58 knockdown, a missense variant that predisposes carriers to inherited MASLD and may promote progression to steatohepatitis. Treatment was associated with lower plasma ALT and AST levels, reduced hepatic steatosis, and fewer macrophage crown-like structures. In addition, bempedoic acid decreased lipid-droplet triglycerides, free cholesterol, cholesteryl esters, and total cholesterol, supporting the concept that inhibition of hepatic cholesterol synthesis may alleviate steatohepatitis by limiting cholesterol accumulation within lipid droplets. Overall, these findings suggest that the hepatoprotective effects of bempedoic acid are related not only to reduced cholesterol synthesis, but also to a favourable reduction in hepatic lipid-droplet lipid burden, including liver fat [76].

An answer is expected from the B-LIFT trial (Effect of Bempedoic Acid on Liver Fat in Individuals With Nonalcoholic Fatty Liver Disease and Type 2 Diabetes; NCT06035874), which is evaluating the effect of bempedoic acid (180 mg/day) on changes in liver fat content from baseline to 24 weeks in individuals with MASLD. Hepatic steatosis will be assessed by magnetic resonance imaging proton density fat fraction (MRI-PDFF), while controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) will be evaluated using FibroScan.

6. Genetic evidence linking ACLY to metabolic disease

Genetic studies have provided important, although sometimes context-dependent, support for ACLY as a causal regulator of lipid and metabolic disease. The first evidence for an essential role of ACLY came from global Acly knockout models, in which homozygous Acly deficiency caused early embryonic lethality, consistent with the central role of ACLY-derived acetyl-CoA in anabolic metabolism and development. In contrast, heterozygous Acly-deficient mice were viable, fertile and normolipidemic on both chow and high-fat diets, despite expressing approximately half-normal amounts of Acly mRNA and protein, suggesting that partial reduction of ACLY activity may be tolerated and that compensatory mechanisms can preserve lipid homeostasis under basal conditions [77].

In a hepatic knockdown model, ACLY abrogation reduced hepatic acetyl-CoA and malonyl-CoA and lowered circulating triglycerides and free fatty acids. It also reduced VLDL-triglyceride secretion and increased hepatic triglyceride accumulation, indicating that ACLY deficiency may alter both lipid synthesis and lipid export in a diet-dependent manner [78].

More recent studies, as reported in Section 5, have refined this view by showing that the metabolic consequences of ACLY loss depend strongly on nutritional context, disease stage and compensatory acetyl-CoA-producing pathways [8].

Guo et al. identified a post-translational mechanism by which ACLY is functionally upregulated during NAFLD progression. In mouse models of hepatic steatosis and in liver samples from patients with NAFLD, hepatic ACLY protein abundance and ACLY acetylation at Lys540, Lys546 and Lys554 were increased, whereas the ACLY deacetylase SIRT2 was reduced. Mechanistically, ACLY acetylation stabilized the protein by limiting ubiquitin–proteasome-mediated degradation. In hepatocytes, ACLY knockdown reduced lipid accumulation, whereas re-expression of ACLY restored it; notably, an acetylation-mimetic ACLY−3KQ mutant promoted lipid accumulation more efficiently than wild-type ACLY. Similarly, in high-fat/high-sucrose diet-fed mice, hepatic ACLY knockdown improved steatosis, reduced liver triglycerides, inflammation and ALT levels, whereas re-expression of ACLY−3KQ more strongly restored the steatotic phenotype than wild-type ACLY [79].

Drug-target Mendelian Randomization analyses have further explored the metabolic consequences of genetically proxied ACLY inhibition. One study assessed the impact of genetically predicted ACLY inhibition on anthropometric traits using ACLY-region variants associated with lower ACLY expression and reduced LDL-C levels. In this analysis, genetically predicted ACLY inhibition was associated with a lower waist-to-hip ratio, with consistent results for BMI-adjusted waist-to-hip ratio [80]. In relation to type 2 diabetes, a cis-Mendelian randomization study based on individual-level data from the UK Biobank and Lifelines, complemented by publicly available genome-wide association data, found no evidence that ACLY targeting increases the risk of new-onset type 2 diabetes [81].

Human genetic studies have further strengthened the therapeutic rationale for ACLY inhibition, particularly in cardiovascular disease. In a Mendelian randomization analysis including 654,783 participants including 105,429 participants who had major cardiovascular events, a genetic score designed to mimic ACLY inhibition was associated with lower LDL-C and with a reduced risk of major cardiovascular events. Per 10 mg/dL genetically predicted reduction in LDL-C, the odds ratio for cardiovascular events was 0.823 for the ACLY score, closely resembling the effect estimated for an HMGCR genetic score, thereby supporting ACLY as a genetically validated lipid-lowering target. Importantly, the same analysis did not identify an increased cancer risk associated with genetically proxied lifelong ACLY inhibition [82]. Finally, regarding aortic stenosis, a drug-target Mendelian randomization analysis identified a single SNP, rs13412, located upstream of the ACLY gene, as a proxy for bempedoic acid exposure. This genetic proxy was significantly associated with a lower risk of aortic stenosis (OR 0.005, 95% CI 0.0002–0.12; P = 0.0009), although the finding should be interpreted cautiously given that it was based on only one instrumental variant [83].

7. Nuclear ACLY: a key regulator of epigenetic control in cancer

7.1. ACLY nuclear localization

Although ACLY is primarily a cytosolic enzyme and is often associated with the endoplasmic reticulum in mammalian cells, accumulating evidence has demonstrated its presence within the nucleus. This dual subcellular distribution highlights the multifunctional nature of ACLY, enabling the enzyme to participate in both metabolic and gene-regulatory processes within distinct cellular compartments.

By generating acetyl-CoA from citrate at a nuclear level, ACLY integrates nutrient catabolism—including glucose, glutamine, and fatty acid metabolism—with anabolic pathways and epigenetic regulation. In

particular, ACLY-derived acetyl-CoA provides the acetyl groups required for histone acetylation, a fundamental chromatin modification that facilitates DNA transcription, replication, and other nuclear processes. A foundational study demonstrated that siRNA-mediated silencing of ACLY significantly reduced global histone acetylation, establishing the enzyme as the primary source of nuclear acetyl-CoA [18].

These findings were subsequently confirmed in genetic models, in which Acly deletion resulted in a striking reduction in global histone acetylation, further demonstrating that ACLY is the predominant supplier of acetyl-CoA for maintaining histone acetylation under physiological conditions [84]. Stable isotope tracing experiments further revealed that ACLY is responsible for the majority of glucose-derived acetyl-CoA incorporated into histones, highlighting its central role in coupling glucose metabolism to chromatin regulation. Although cells lacking ACLY retain the ability to sustain histone acetylation by utilizing acetate as an alternative carbon source, this compensatory pathway becomes significant only in the absence of ACLY, indicating that ACLY is the dominant source of acetyl-CoA for histone acetylation under nutrient-replete conditions [84].

Through this biochemical axis, ACLY directly couples cellular metabolic status, such as glucose availability, to the precise regulation of gene expression and chromatin dynamics.

More recently, ACLY was reported to undergo nuclear translocation in fibroblasts upon fibrotic stimulation, thereby facilitating TGF-beta-mediated myofibroblast activation by promoting histone H3 lysine 27 acetylation (H3K27ac) at fibrotic gene loci. Co-immunoprecipitation assays revealed that ACLY physically interacts with the transcription factors SMAD2/3, directing the enzyme to pro-fibrotic genomic regions to drive localized acetyl-CoA production [85].

The relationship between acetyl-CoA metabolism and histone acetylation is strongly influenced by intracellular compartmentalization, which enables precise spatial and temporal control of chromatin-modifying reactions. While acetyl-CoA produced in the cytoplasm can diffuse through nuclear pores and contribute to the nuclear acetyl-CoA pool, increasing evidence indicates that local acetyl-CoA generation within the nucleus is critical for efficient epigenetic regulation. Although acetyl-CoA can theoretically equilibrate between the cytosolic and nuclear compartments through passive diffusion, the nuclear production of acetyl-CoA appears to provide a strategically important source for chromatin remodelling and transcriptional regulation. The requirement for localized acetyl-CoA production is further supported by the biochemical properties of the molecule itself. Acetyl-CoA contains a high-energy thioester bond whose hydrolysis releases approximately 31.4 kJ/mol of free energy, rendering the molecule metabolically reactive and relatively short-lived. Consequently, cells rely on the compartment-specific synthesis of acetyl-CoA in close proximity to its sites of utilization.

7.2. ACLY in tumorigenesis

ACLY is frequently overexpressed in a wide range of human malignancies, where it supports tumour growth, metabolic adaptation, and cancer stemness, making it an attractive therapeutic target [86]. By catalysing the conversion of citrate into acetyl-CoA, ACLY fulfils a dual function in cancer cells: it provides substrates for de novo lipid biosynthesis while simultaneously supplying acetyl-CoA for protein and histone acetylation, thereby linking cellular metabolism to epigenetic regulation. Consequently, ACLY inhibitors, initially developed for metabolic disorders, have attracted considerable interest as anticancer agents. Although genetic and pharmacological inhibition of ACLY suppresses tumour growth in multiple preclinical models, therapeutic efficacy may be attenuated by compensatory acetyl-CoA-producing pathways, including ACSS2 and PDH, which collectively maintain acetyl-CoA homeostasis under metabolic stress.

A growing body of evidence indicates that many oncogenic functions of ACLY are mediated by its nuclear pool, which generates a localized source of acetyl-CoA to support histone acetylation and transcriptional reprogramming. One notable example involves the tumour suppressor SIRT6, which restricts ACLY nuclear accumulation. Loss of SIRT6 promotes the enrichment of ACLY within the nucleus, increasing nuclear acetyl-CoA availability and global histone acetylation, thereby activating transcriptional programs associated with cell adhesion, migration, and tumorigenesis. These findings identify nuclear ACLY as an important mediator of metabolic–epigenetic coupling in cancer [87].

Recent studies have also implicated ACLY in the development of therapy resistance. In colorectal cancer (CRC), ACLY acts as a central metabolic regulator linking citrate-derived acetyl-CoA production to the epigenetic control of the drug-efflux transporter MDR1/ABCB1. Genetic and pharmacological modulation of ACLY demonstrates that its catalytic activity sustains H3K9 and H4K16 acetylation and promotes MDR1-associated transcriptional programs. Conversely, ACLY inhibition reduces histone acetylation and suppresses the expression of genes involved in chemoresistance. Consistent with these observations, ACLY and MDR1 expression positively correlate in human CRC specimens, particularly in advanced-stage disease, highlighting an ACLY-dependent metabolic–epigenetic axis that may be exploited therapeutically to overcome drug resistance [88].

In addition to its nuclear functions, ACLY contributes to tumour adaptation through regulation of cytosolic acetyl-CoA signalling. Recent work has demonstrated that depletion of the cytosolic acetyl-CoA pool, induced by fasting, pharmacological inhibition of ACLY, or targeted therapies that impair nutrient uptake, triggers NLRX1-dependent mitophagy. In KRAS-mutant tumours, inhibition of oncogenic signalling causes a profound reduction in cytosolic acetyl-CoA levels, activating NLRX1, a mitochondria-associated metabolic sensor recently shown to directly bind acetyl-CoA. Activation of the acetyl-CoA–NLRX1 axis promotes mitochondrial quality control through mitophagy, thereby limiting oxidative stress and enhancing cancer-cell survival under therapeutic pressure. This adaptive response contributes to resistance against KRAS-targeted therapies and reveals an unexpected signalling role for acetyl-CoA beyond its metabolic functions [89].

Beyond solid tumours, ACLY has also emerged as a critical regulator of inflammatory and metabolic reprogramming in hematologic malignancies. In TET2-mutant myeloid cells, dysregulated O-GlcNAc transferase (OGT) activity enhances O-GlcNAcylation of ACLY, increasing its enzymatic activity and promoting lipogenic and inflammatory programs. This hyperactivated OGT–ACLY axis links epigenetic deregulation to inflammasome activation and lipid accumulation. Importantly, genetic or pharmacological inhibition of ACLY attenuates inflammatory signalling and suppresses pathological immune activation, identifying ACLY as a potential therapeutic target in TET2-deficient clonal haematopoiesis and myeloid disorders [90].

ACLY has also been implicated in lymphoid malignancies through its ability to regulate metabolite-dependent epigenetic remodelling. In PD−1-deficient T-cell non-Hodgkin lymphomas, increased glycolytic flux leads to citrate accumulation and enhanced ACLY-dependent acetyl-CoA production. Elevated acetyl-CoA availability promotes histone acetylation and chromatin remodelling at AP−1-responsive loci, driving persistent AP−1 activation and tumour growth. Pharmacological inhibition of ACLY suppresses AP−1 signalling and selectively impairs the growth of PD−1-deficient lymphoma cells, identifying ACLY as a potential therapeutic target in this setting [91].

7.3. ACLY in hepatocellular carcinoma

Recent studies have highlighted a particularly important role for ACLY in hepatocellular carcinoma (HCC), where it contributes to both therapeutic resistance and tumour progression. One mechanism involves chemotherapy-induced stabilization of nuclear ACLY. NAT10, a nuclear acetyltransferase, directly interacts with ACLY and acetylates it at lysine 468 in response to chemotherapeutic stress. This modification protects ACLY from SQSTM1-mediated proteasomal degradation and

promotes its nuclear accumulation. Increased nuclear ACLY activity enhances local acetyl-CoA production and stimulates H3K27 acetylation at target loci, resulting in transcriptional activation of genes including CYP2C9 and PIK3R1. Through this mechanism, the NAT10–ACLY axis promotes adaptive transcriptional responses that contribute to chemotherapy resistance in HCC [92].

A second line of evidence has established ACLY as a therapeutic vulnerability in MASH-associated HCC. Using genetically engineered mouse models that recapitulate human disease, hepatocyte- and tumour-specific deletion of ACLY reduced neoplastic lesion formation by more than 70%, indicating a critical requirement for ACLY during tumour development. To therapeutically exploit this dependency, investigators used EVT0185, a novel ACLY inhibitor that is metabolically activated in the liver by SLC27A2 to generate a CoA-thioester metabolite capable of directly binding the ACLY CoA-binding pocket. Oral administration of EVT0185 markedly reduced tumour burden across multiple MASH-HCC models and enhanced the efficacy of standard treatments, including tyrosine kinase inhibitors and immune checkpoint-based therapies. Mechanistically, integrated transcriptomic and spatial analyses linked ACLY inhibition to increased expression of CXCL13, enhanced B-cell infiltration, and the formation of tertiary lymphoid structures (TLSs) within tumours. Although the precise molecular mechanisms remain incompletely understood, these findings suggest that ACLY inhibition reshapes the tumour microenvironment toward a more immunogenic state, potentially through alterations in metabolite availability and chromatin acetylation. Collectively, these data identify ACLY as both a driver of tumour progression and a promising therapeutic target in MASH-associated HCC [10].

7.4. ACLY, tumour immunity, and immunotherapy

Beyond its direct effects on tumour-cell metabolism, ACLY has emerged as an important regulator of antitumor immunity. In macrophages, ACLY participates in the transcriptional control of inflammatory responses through both metabolic and epigenetic mechanisms. Santarsiero and colleagues demonstrated that activated macrophages accumulate ACLY in the nucleus, where locally generated acetyl-CoA supports acetylation of the NF-κB subunit p65 and promotes the transcription of pro-inflammatory genes, including IL1B and PTGS2. Pharmacological inhibition of ACLY reduced NF-κB promoter occupancy and attenuated inflammatory gene expression, highlighting the importance of ACLY-dependent acetyl-CoA production in macrophage activation [93].

Consistent with these findings, similar mechanisms have recently been described in macrophages isolated from patients with MASH and in hepatocytes exposed to the inflammatory cytokine TNF-α. Pharmacological inhibition of ACLY alleviated lipid accumulation, reduced oxidative stress, and decreased the secretion of pro-inflammatory cytokines. Mechanistically, ACLY inhibition reduced NF-κB nuclear translocation and global histone acetylation, thereby dampening inflammatory gene expression. Conversely, inflammatory stimulation induced ACLY overexpression through NF-κB binding to the ACLY promoter, suggesting the existence of a positive feed-forward loop that sustains inflammatory signalling [94].

Additional studies have revealed a critical role for ACLY in macrophage polarization within the tumour microenvironment. Lactate-driven differentiation of macrophages toward an immunosuppressive M2 phenotype requires mitochondrial pyruvate metabolism and ACLY activity. Inhibition of either mitochondrial pyruvate transport or ACLY impairs histone acetylation and M2 polarization, whereas exogenous acetate restores both processes. Consistent with these findings, conditional deletion of ACLY in macrophages suppresses M2-dependent tumour progression, supporting the concept that metabolic control of histone acetylation contributes to immune evasion within tumours [95].

The relationship between ACLY and antitumor immunity is complex and context dependent. Recent work demonstrated that ACLY inhibition promotes lipid peroxidation of polyunsaturated fatty acids (PUFAs), leading to activation of the cGAS–STING pathway and induction of PD-L1 expression. In human tumours, low ACLY expression correlates with cGAS–STING activation and increased infiltration of exhausted T cells. Importantly, despite increasing PD-L1 levels, ACLY inhibition sensitizes tumours to anti-PD-L1 therapy in a cGAS-dependent manner. Dietary PUFA supplementation was sufficient to recapitulate this effect, suggesting that modulation of ACLY-dependent lipid metabolism may enhance the efficacy of immune checkpoint blockade in otherwise resistant tumours [96].

Collectively, these studies expand the role of ACLY beyond its traditional function as a metabolic enzyme and establish it as a critical regulator of tumour–immune interactions. Depending on cellular context, ACLY influences inflammatory signalling, macrophage polarization, immune checkpoint responses, and adaptive antitumor immunity. These observations suggest that targeting ACLY may not only suppress tumour growth directly but also reshape the tumour microenvironment and improve responsiveness to immunotherapy.

8. Conclusions

ACLY inhibition has progressed from lipid-lowering strategy to a broader therapeutic concept linking acetyl-CoA metabolism with cardiovascular disease, MASLD and cancer biology. Its most established role remains in LDL-C lowering and cardiovascular risk reduction, where bempedoic acid provides clinical proof of concept and is supported by outcome data. In MASLD/MASH, ACLY targeting is promising but still emerging: preclinical evidence suggests benefits on steatosis, inflammation and fibrosis, although these effects may reflect both reduced *de novo* lipogenesis through ACLY inhibition and ACLY-independent activation of PPARα by parent bempedoic acid, with compensatory pathways such as ACSS2-dependent acetate metabolism potentially limiting or reshaping responses. More broadly, the discovery of nuclear functions of ACLY has fundamentally expanded our understanding of how metabolic enzymes regulate gene expression. ACLY functions as a metabolic–epigenetic integrator that coordinates nutrient availability with chromatin remodelling, transcriptional programs and immune responses. Consequently, dysregulated ACLY activity contributes to multiple hallmarks of cancer, including tumour growth, therapy resistance, metabolic plasticity, immune evasion, and tumour-promoting inflammation. The increasing availability of selective ACLY inhibitors, together with emerging evidence from preclinical cancer models, supports the notion that ACLY represents a promising therapeutic target. Future studies should define the relative contribution of ACLY-dependent and ACLY-independent mechanisms, identify compensatory metabolic circuits, clarify tissue- and compartment-specific effects, and establish whether the encouraging preclinical findings in MASLD and cancer translate into durable clinical benefit.

CRediT authorship contribution statement

Alberto Corsini: Writing – review & editing. **Nico Mitro:** Writing – review & editing. **Silvia Pedretti:** Writing – original draft. **Serena Ghisletti:** Writing – review & editing, Writing – original draft, Methodology. **Chiara Macchi:** Writing – original draft. **Massimiliano Ruscica:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Cesare R Sirtori:** Writing – original draft, Conceptualization.

Funding

This work was partially supported by European Union Marie Skłodowska-Curie Actions Doctoral Networks grant 101167421 (M.R. and C. M.); by Progetto ANTHEM–AdvaNced Technology for Human centEred Medicine PNC0000003, Ministry of University (M.R.); by Fondo di Beneficenza di Intesa Sanpaolo, grant B/2025/0265 (M.R.); by Italian

Ministry of Health (Ministero della Salute), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Ricerca Corrente 2026 (M.R.); by the Ministry of University and Research (MUR) Progetto Eccellenza (2023–2027) to the Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti," Università degli Studi di Milano; by the Italian Ministry of Health with the Ricerca Corrente and 5 × 1000 funds to the IEO IRCCS (N.M.); by the Italian Association for Cancer Research (AIRC grant IG 24506) to S.G. and AIRC grant IG 23127 to N.M. and by the Italian Ministry of Health EP PerMed (GA N° 101137129 of the EU Horizon Europe Research and Innovation Programme, CERP-2025-23687593) to S.G.

Declaration of Competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alberto Corsini has received research funding and/or honoraria from Amgen, Daiichi-Sankyo Europe, Amarin, DOC, MSD, Novartis, Recordati Spa, Sanofi, and Viatris.

Data availability

No data was used for the research described in the article.

References

[1] C.T. Cramer, B. Goetz, K.L. Hopson, G.J. Fici, R.M. Ackermann, S.C. Brown, C. L. Bisgaier, W.G. Rajeswaran, D.C. Oniciu, M.E. Pape, Effects of a novel dual lipid synthesis inhibitor and its potential utility in treating dyslipidemia and metabolic syndrome, J. Lipid Res. 45 (7) (2004) 1289–1301.

[2] S.L. Pinkosky, S. Filippov, R.A. Srivastava, J.C. Hanselman, C.D. Bradshaw, T. R. Hurley, C.T. Cramer, M.A. Spahr, A.F. Brant, J.L. Houghton, C. Baker, M. Naples, K. Adeli, R.S. Newton, AMP-activated protein kinase and ATP-citrate lyase are two distinct molecular targets for ETC-1002, a novel small molecule regulator of lipid and carbohydrate metabolism, J. Lipid Res. 54 (1) (2013) 134–151.

[3] S.L. Pinkosky, R.S. Newton, E.A. Day, R.J. Ford, S. Lhotak, R.C. Austin, C.M. Birch, B.K. Smith, S. Filippov, P.H.E. Groot, G.R. Steinberg, N.D. Lalwani, Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis, Nat. Commun. 7 (2016) 13457.

[4] M. Ruscica, N. Ferri, M. Banach, C.R. Sirtori, A. Corsini, Side effects of statins: from pathophysiology and epidemiology to diagnostic and therapeutic implications, Cardiovasc. Res. 118 (17) (2023) 3288–3304.

[5] A. Sayed, O. Shazly, L. Slipczuk, C. Krittanawong, F. Baloch, S.S. Virani, The clinical efficacy and safety of bempedoic acid in patients at elevated risk of cardiovascular disease: a meta-analysis of randomized clinical trials, Cardiovasc. Drugs Ther. 38 (6) (2024) 1415–1420.

[6] S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P. D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D. E. Grobbee, M.J. Louie, C.F. Chen, N. Li, L. Bloedon, P. Robinson, M. Horner, W. J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, S.J. Nicholls, Investigators CO. Bempedoic Acid and cardiovascular outcomes in statin-intolerant patients, N. Engl. J. Med. 388 (15) (2023) 1353–1364.

[7] J.G. Supplee, R. Marmorstein, K.E. Wellen, Molecular targets of bempedoic acid and related decoy fatty acids, Trends Endocrinol. Metab. 36 (10) (2025) 917–928.

[8] M.R. Morrow, B. Batchuluun, J. Wu, E. Ahmadi, J.M. Leroux, P. Mohammadi-Shemirani, E.M. Desjardins, Z. Wang, E.E. Tsakiridis, D.C.T. Lavoie, A. Reihani, B. K. Smith, J.M. Kwiecien, J.S.V. Lally, T.L. Nero, M.W. Parker, K. Ask, J.W. Scott, L. Jiang, G. Pare, S.L. Pinkosky, G.R. Steinberg, Inhibition of ATP-citrate lyase improves NASH, liver fibrosis, and dyslipidemia, Cell. Metab. 34 (6) (2022) 919–936, e918.

[9] Z. Xie, L. Cheng, Y. Hu, G. Song, F. Wang, M. Zhang, Y. Zhang, X. Zhang, C. Zhou, X. Zhu, X. Sun, H. Xu, Q. Song, Y. Yang, J. Zheng, S. Ji, J. Ye, C. Zhou, X. Lai, W. Li, Y. Zhang, X. Chen, J. Niu, Y. Ding, F. Nan, J. Li, The enedioic acid analog 326E alleviates metabolic dysfunction-associated steatohepatitis via dual targeting at ACLY and PPARalpha, Cell. Metab. 37 (11) (2025) 2149–2166, e2149.

[10] J. Gautam, J. Wu, J.S.V. Lally, J.D. McNicol, R. Fayyazi, E. Ahmadi, D.C. Oniciu, S. Heaton, R.S. Newton, S. Rehal, D. Bhattacharya, F. Di Pastena, B. Nguyen, C. M. Valvano, L.K. Townsend, S. Banskota, B. Batchuluun, M.J.T. Jabile, A. Payne, J. Lu, E.M. Desjardins, N. Kubota, E.E. Tsakiridis, B. Mistry, A. Aganostopoulos, V. Houde, A. Dansercoer, K.H.G. Verschueren, S.N. Savvides, J.A. Hammill, K. Bezverbnaya, P. Muti, T. Tsakiridis, W. Dai, L. Jiang, Y. Hoshida, M. Larche, J. L. Bramson, S.L. Friedman, K. Verstraete, D. Wang, G.R. Steinberg, ACLY inhibition promotes tumour immunity and suppresses liver cancer, Nature 645 (8080) (2025) 507–517.

[11] C. Papa, A. Rose, H.N.G. Martin, A. Useini, F. Geier, L. Liao, J.R. Rodriguez-Aguilera, P. Valina-Allo, A. Hoffmann, A. Tvardovskiy, F. Zulfqar, A. Zimmerman, G. Schicht, F. Ott, C. Korner, B. Engelmann, U. Rolle-Kampczyk, M. von Bergen, M. Meier, T. Bartke, D. Seehofer, N. Kloting, M. Matz-Soja, G. Damm, J.N. Boeckel, J.M. Buescher, M. Bluher, U. Laufs, O. Bondareva, N. Strater, G. Kunze, J.T. Heiker, B.N. Sheikh, Bempedoic acid directly binds and activates PPARalpha, Cell. Metab. 38 (4) (2026) 824–830, e825.

[12] S. Ghisletti, M. Russo, TCA-cycle metabolites in the nucleus: drivers of chromatin and epigenetic control, BMC Biol. 23 (1) (2025) 316.

[13] Y. Zang, M. Shi, L. Tai, Y. Hu, Y. Wang, R. Zheng, Z. Feng, H. Yuan, X. Wen, L. Dai, Design, synthesis, and Biological evaluation of novel macrocyclic derivatives as potent ATP-citrate lyase inhibitors, Eur. J. Med. Chem. 292 (2025) 117684.

[14] K.H.G. Verschueren, C. Blanchet, J. Felix, A. Dansercoer, D. De Vos, Y. Bloch, J. Van Beeumen, D. Svergun, I. Gutsche, S.N. Savvides, K. Verstraete, Structure of ATP citrate lyase and the origin of citrate synthase in the Krebs cycle, Nature 568 (7753) (2019) 571–575.

[15] N.A. Elshourbagy, J.C. Near, P.J. Kmetz, G.M. Sathe, C. Southan, J.E. Strickler, M. Gross, J.F. Young, T.N. Wells, P.H. Groot, Rat ATP citrate-lyase. Molecular cloning and sequence analysis of a full-length cDNA and mRNA abundance as a function of diet, organ, and age, J. Biol. Chem. 265 (3) (1990) 1430–1435.

[16] M. Chypre, N. Zaidi, K. Smans, ATP-citrate lyase: a mini-review, Biochem. Biophys. Res. Commun. 422 (1) (2012) 1–4.

[17] F. Fan, H.J. Williams, J.G. Boyer, T.L. Graham, H. Zhao, R. Lehr, H. Qi, B. Schwartz, F.M. Raushel, T.D. Meek, On the catalytic mechanism of human ATP citrate lyase, Biochemistry 51 (25) (2012) 5198–5211.

[18] K.E. Wellen, G. Hatzivassiliou, U.M. Sachdeva, T.V. Bui, J.R. Cross, C.B. Thompson, ATP-citrate lyase links cellular metabolism to histone acetylation, Science 324 (5930) (2009) 1076–1080.

[19] G. Sutendra, A. Kinnaird, P. Dromparis, R. Paulin, T.H. Stenson, A. Haromy, K. Hashimoto, N. Zhang, E. Flaim, E.D. Michelakis, A nuclear pyruvate dehydrogenase complex is important for the generation of acetyl-CoA and histone acetylation, Cell 158 (1) (2014) 84–97.

[20] R. Nagaraj, M.S. Sharpley, F. Chi, D. Braas, Y. Zhou, R. Kim, A.T. Clark, U. Banerjee, Nuclear localization of mitochondrial TCA cycle enzymes as a critical step in mammalian zygotic genome activation, Cell 168 (1-2) (2017) 210–223, e211.

[21] Y. Wang, Y.R. Guo, K. Liu, Z. Yin, R. Liu, Y. Xia, L. Tan, P. Yang, J.H. Lee, X.J. Li, D. Hawke, Y. Zheng, X. Qian, J. Lyu, J. He, D. Xing, Y.J. Tao, Z. Lu, KAT2A coupled with the alpha-KGDH complex acts as a histone H3 succinyltransferase, Nature 552 (7684) (2017) 273–277.

[22] J. Chen, I. Guccini, D. Di Mitri, D. Brina, A. Revandkar, M. Sarti, E. Pasquini, A. Alajati, S. Pinton, M. Losa, G. Civenni, C.V. Catapano, J. Sgrignani, A. Cavalli, R. D'Antuono, J.M. Asara, A. Morandi, P. Chiarugi, S. Crotti, M. Agostini, M. Montopoli, I. Masgras, A. Rasola, R. Garcia-Escudero, N. Delaleu, A. Rinaldi, F. Bertoni, J. Bono, A. Carracedo, A. Alimonti, Compartmentalized activities of the pyruvate dehydrogenase complex sustain lipogenesis in prostate cancer, Nat. Genet. 50 (2) (2018) 219–228.

[23] W. Zhou, Z.W. Nie, D.J. Zhou, X.S. Cui, Acetyl-CoA synthases are essential for maintaining histone acetylation under metabolic stress during zygotic genome activation in pigs, J. Cell. Physiol. 236 (10) (2021) 6948–6962.

[24] M. Russo, F. Pileri, S. Ghisletti, Novel insights into the role of acetyl-CoA producing enzymes in epigenetic regulation, Front. Endocrinol. (Lausanne) 14 (2023) 1272646.

[25] M. Russo, F. Gualdrini, V. Vallelonga, E. Prosperini, R. Noberini, S. Pedretti, C. Borriero, P. Di Chiaro, S. Polletti, G. Imperato, M. Marenda, C. Ghirardi, F. Bedin, A. Cuomo, S. Rodighiero, T. Bonaldi, N. Mitro, S. Ghisletti, G. Natoli, Acetyl-CoA production by Mediator-bound 2-ketoacid dehydrogenases boosts de novo histone acetylation and is regulated by nitric oxide, Mol. Cell. 84 (5) (2024) 967–980, e910.

[26] X. Fu, Y. Zhu, X. Lu, X. Gao, L. Xin, Y. Ren, X. Liu, L. Ge, J. Hao, Z. Yao, L. Shi, J. Yang, ACSS1 co-opts acetyl-CoA metabolism to drive DNA repair and undermine radiotherapy efficacy in breast cancer, Cell. Death Dis. 17 (1) (2025) 119.

[27] N.J. Pearce, J.W. Yates, T.A. Berkhout, B. Jackson, D. Tew, H. Boyd, P. Camilleri, P. Sweeney, A.D. Gribble, A. Shaw, P.H. Groot, The role of ATP citrate-lyase in the metabolic regulation of plasma lipids. Hypolipidaemic effects of SB-204990, a lactone prodrug of the potent ATP citrate-lyase inhibitor SB-201076, Biochem. J. 334 (Pt 1) (1998) 113–119. Pt 1.

[28] J.J. Li, H. Wang, J.A. Tino, J.A. Robl, T.F. Herpin, R.M. Lawrence, S. Biller, H. Jamil, R. Ponticiello, L. Chen, C.H. Chu, N. Flynn, D. Cheng, R. Zhao, B. Chen, D. Schnur, M.T. Obermeier, V. Sasseville, R. Padmanabha, K. Pike, T. Harrity, 2-hydroxy-N-arylbenzenesulfonamides as ATP-citrate lyase inhibitors, Bioorg. Med. Chem. Lett. 17 (11) (2007) 3208–3211.

[29] Z. Zhan, A. Li, W. Zhang, X. Wu, J. He, Z. Li, Y. Li, J. Sun, H. Zhang, ATP-citrate lyase inhibitor improves ectopic lipid accumulation in the kidney in a db/db mouse model, Front. Endocrinol. (Lausanne) 13 (2022) 914865.

[30] J. Wei, S. Leit, J. Kuai, E. Therrien, S. Rafi, H.J. Harwood Jr., B. DeLaBarre, L. Tong, An allosteric mechanism for potent inhibition of human ATP-citrate lyase, Nature 568 (7753) (2019) 566–570.

[31] Z. Xie, M. Zhang, Q. Song, L. Cheng, X. Zhang, G. Song, X. Sun, M. Gu, C. Zhou, Y. Zhang, K. Zhu, J. Yin, X. Chen, J. Li, F. Nan, Development of the novel ACLY inhibitor 326E as a promising treatment for hypercholesterolemia, Acta Pharm. Sin. B 13 (2) (2023) 739–753.

[32] M. Chen, P.J. Little, S. Kong, M. Banach, J. Weng, S. Xu, Aclysiran, an RNAi therapeutic agent targeting ACLY, treats hypercholesterolemia and atherosclerosis in ApoE (-/-) mice, Acta Pharm. Sin. B 14 (12) (2024) 5505–5508.

[33] K. Phutela, A. Bal, N. Singh, S. Sharma, Hydroxycitrate-loaded exosomes demonstrate enhanced therapeutic efficacy against lung adenocarcinoma by inhibiting the metabolic enzyme ATP citrate lyase, Nanoscale Adv. 7 (12) (2025) 3846–3858.

[34] Z. Zhang, M. Chen, Y. Xu, Z. Wang, Z. Liu, C. He, F. Zhang, X. Feng, X. Ni, Y. Chen, J. Wang, X. Liang, Z. Xie, J. Li, M. Banach, J. Pelisek, Y. Huo, Y. Hu, P.C. Evans, L. Wang, X.Y. Tian, J. Xiao, Y. Shang, Y. Zheng, X. Xian, J. Weng, S. Xu, A natural small molecule isoginkgetin alleviates hypercholesterolemia and atherosclerosis by targeting ACLY, Theranostics 15 (10) (2025) 4325–4344.
[35] X. Xu, Z. Wang, H. Wen, X. Xie, T. Hou, F. Luo, H. Zhou, J. Wang, Y. Zhao, X. Liang, Design and synthesis of novel ATP-citrate lyase inhibitors and their effects on MAFLD/MASH, Eur. J. Med. Chem. 310 (2026) 118796.
[36] M. Ruscica, C.R. Sirtori, S. Carugo, M. Banach, A. Corsini, Bempedoic acid: for whom and when, Curr. Atheroscler. Rep. 24 (10) (2022) 791–801.
[37] C.M. Ballantyne, G.D. Norata, The evolving landscape of targets for lipid lowering: from molecular mechanisms to translational implications, Eur. Heart J. 46 (44) (2025) 4737–4750.
[38] D. Henry, E. Bauge, B. Staels, F. Lalloyer, The evolution of lipid-lowering drugs in the management of cardiovascular disease risk: from the first cardiovascular disease risk-reducing therapies to the novel challenging strategies, Pharmacol. Rev. 77 (6) (2025) 100086.
[39] D.K. Kalra, K.K. Ray, A. Bajaj, P.R. Kushner, M.L. Wilcox, M.R. Dicklin, C. F. Kirkpatrick, K.C. Maki, Low-density lipoprotein cholesterol lowering and risk of major adverse cardiovascular events in primary prevention trials: a meta-analysis, J. Clin. Lipidol. 20 (4) (2026) 738–749.
[40] A. Pirillo, M. Casula, E. Olmastroni, S. Scotti, A. Corsini, A.L. Catapano, Are we underestimating the benefits of lipid-lowering therapies? Pharmacol. Rev. 78 (4) (2026) 100140.
[41] S.E. Nissen, V. Menon, S.J. Nicholls, D. Brennan, L. Laffin, P. Ridker, K.K. Ray, D. Mason, J.J.P. Kastelein, L. Cho, P. Libby, N. Li, J. Foody, M.J. Louie, A. M. Lincoff, Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients, JAMA 330 (2) (2023) 131–140.
[42] F. Rodriguez, L. Cho, J. Foody, A.M. Lincoff, L. Lei, S.J. Nicholls, S.E. Nissen, H. A. Powell, J. Plutzky, Characteristics and outcomes for hispanic/latinx participants with statin intolerance receiving bempedoic acid, J. Am. Coll. Cardiol. 83 (21) (2024) 2130–2132.
[43] L. Cho, J. Plutzky, D. Brennan, M.J. Louie, L. Lei, P. Robinson, H.A. Powell, S. J. Nicholls, A.M. Lincoff, S.E. Nissen, Impact of bempedoic acid on cardiovascular outcomes by sex, Circulation 149 (22) (2024) 1775–1777.
[44] F. Mach, K.C. Koskinas, J.E. Roeters van Lennep, L. Tokgozoglu, L. Badimon, C. Baigent, M. Benn, C.J. Binder, A.L. Catapano, G.G. De Backer, V. Delgado, N. Fabin, B.A. Ference, I.M. Graham, U. Landmesser, U. Laufs, B. Mihaylova, B. G. Nordestgaard, D.J. Richter, M.S. Sabatine, Group EESD, 2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias, Atherosclerosis 409 (2025) 120479.
[45] M. Writing Committee, R.S. Blumenthal, P.B. Morris, M. Gaudino, H.M. Johnson, T. S. Anderson, V.A. Bittner, R. Blankstein, L.C. Brewer, L. Cho, S.D. de Ferranti, E. Gianos, T.J. Gluckman, K.F. Gradney, I. Isiadinso, D.M. Lloyd-Jones, J.C. Marrs, S.S. Martin, K.H. McLain, L.S. Mehta, S. Mora, W.M. Mulugeta, P. Natarajan, A. M. Navar, C.E. Orringer, T.S. Polonsky, H.R. Reynolds, J.J. Saseen, M.D. Shapiro, D.E. Soffer, S.A. Tynes, C.D. Villavaso, S.S. Virani, J.T. Wilkins, 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of dyslipidemia: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, Circulation 153 (17) (2026) e1154–e1276.
[46] S.J. Nicholls, A.J. Nelson, A.M. Lincoff, D. Brennan, K.K. Ray, L. Cho, V. Menon, N. Li, L. Bloedon, S.E. Nissen, Impact of bempedoic acid on total cardiovascular events: a prespecified analysis of the CLEAR outcomes randomized clinical trial, JAMA Cardiol. 9 (3) (2024) 245–253.
[47] A.M. Lincoff, K.K. Ray, W.J. Sasiela, T. Haddad, S.J. Nicholls, N. Li, L. Cho, D. Mason, P. Libby, S.G. Goodman, S.E. Nissen, Comparative cardiovascular benefits of bempedoic acid and statin drugs, J. Am. Coll. Cardiol. 84 (2) (2024) 152–162.
[48] S. Raghavan, J.L. Vassy, Y.L. Ho, R.J. Song, D.R. Gagnon, K. Cho, P.W.F. Wilson, L. S. Phillips, Diabetes mellitus-related all-cause and cardiovascular mortality in a national cohort of adults, J. Am. Heart Assoc. 8 (4) (2019) e011295.
[49] K.K. Ray, S.J. Nicholls, N. Li, M.J. Louie, D. Brennan, A.M. Lincoff, S.E. Nissen, Committees CO, Investigators. Efficacy and safety of bempedoic acid among patients with and without diabetes: prespecified analysis of the CLEAR Outcomes randomised trial, Lancet Diabetes Endocrinol. 12 (1) (2024) 19–28.
[50] M. Federici, R. Buzzetti, R. Candido, S. De Cosmo, A. Pirillo, G. Russo, G. Sesti, A. Avogaro, The role of bempedoic acid in the management of dyslipidaemia in people with diabetes: an expert opinion of Italian diabetologists, Cardiovasc. Diabetol. 25 (1) (2026).
[51] H.E. Bays, L. Bloedon, D. Brennan, L. Lei, A.M. Lincoff, S.J. Nicholls, J. Plutzky, H. A. Powell, S.E. Nissen, Bempedoic acid for prevention of cardiovascular events in people with obesity: a CLEAR outcomes subset analysis, J. Am. Heart Assoc. 14 (4) (2025) e037898.
[52] H.E. Bays, S. Bindlish, T.L. Clayton, Obesity, diabetes mellitus, and cardiometabolic risk: an Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2023, Obes. Pillars 5 (2023) 100056.
[53] H. Al Kayed, R. Rajesh, A. Shaikh, R. Martins, B. Alrabadi, Lipid and anti-inflammatory effects of bempedoic acid across treatment regimens: a harmonized meta-analysis of randomized trials, J. Clin. Lipidol. (2026).
[54] Z.M. Younossi, P. Golabi, J.M. Paik, A. Henry, C. Van Dongen, L. Henry, The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review, Hepatology 77 (4) (2023) 1335–1347.
[55] V.D. de Jong, S.E. Nissen, W.J. Sasiela, M. Li, L. Bloedon, A.M. Lincoff, S. J. Nicholls, M.C. Cabezas, Grobbee DE, Effect of bempedoic acid on cardiovascular risk in patients with metabolic dysfunction-associated steatotic liver disease, Eur. J. Prev. Cardiol. (2026).
[56] B.F. Spiazzi, D. Brennan, C.P. Zingano, H.A. Powell, S.J. Nicholls, S.E. Nissen, L. J. Laffin, Bempedoic acid and venous thromboembolism risk among statin-intolerant patients: a post hoc analysis of the CLEAR outcomes randomized clinical trial, JAMA Cardiol. (2026).
[57] K.K. Ray, S.J. Nicholls, A.M. Lincoff, N. Li, H.A. Powell, P.M. Herout, L. Bloedon, S. E. Nissen, Association of uric acid-lowering therapies on gout frequency with bempedoic acid: clinical insights from CLEAR outcomes, JACC Adv. 4 (11 Pt 1) (2025) 102207.
[58] H.E. Bays, L.T. Bloedon, G. Lin, H.A. Powell, M.J. Louie, S.J. Nicholls, A.M. Lincoff, S.E. Nissen, Safety of bempedoic acid in patients at high cardiovascular risk and with statin intolerance, J. Clin. Lipidol. 18 (1) (2024) e59–e69.
[59] A. Di Ciaula, M. Khalil, G. Garruti, P. Portincasa, Bempedoic acid within the phase ternary diagram governing biliary cholesterol solubilization and gallstone risk, J. Lipid Res. (2026) 101056.
[60] N. Ferri, A. Corsini, Mechanism of bempedoic acid induced cholelithiasis: a role for statins to limit this adverse effect? Pharmacol. Res. 196 (2023) 106900.
[61] C. Macchi, I. Fichtner, T. Mohamed, E. Franchi, A.S. Rizzuto, C. Pavanello, J. Gindlhuber, S. Nerini, C.R. Sirtori, E. Osto, S. Carugo, M. Busnelli, G. Chiesa, V. Magnaghi, A. Corsini, M. Ruscica, Inhibition of ATP citrate lyase does not affect muscle mitochondrial activity in apoE(-/-) mice, Biomed. Pharmacother. 193 (2025) 118726.
[62] P.S. Chen, M. Lee, S.C. Tang, P.H. Huang, H.I. Yeh, C. Jia-Yin Hou, I.C. Hsieh, J. T. Lee, J.S. Jeng, Y.H. Li, 2022 focused update of the 2017 Taiwan lipid guidelines for high risk patients: coronary artery disease, peripheral artery disease and ischemic stroke, J. Formos. Med. Assoc. 121 (8) (2022) 1363–1370.
[63] P.H. Huang, Y.W. Lu, Y.L. Tsai, Y.W. Wu, H.Y. Li, H.Y. Chang, C.H. Wu, C.Y. Yang, D.C. Tarng, C.C. Huang, L.T. Ho, C.F. Lin, S.C. Chien, Y.J. Wu, H.I. Yeh, W.H. Pan, Y.H. Li, expert committee for the Taiwan Lipid Guidelines for Primary P. 2022 Taiwan lipid guidelines for primary prevention, J. Formos. Med. Assoc. 121 (12) (2022) 2393–2407.
[64] I.C. Hsieh, D.Y. Chen, C.S. Chu, Y.Y. Chang, B.H. Tzeng, T.C. Huang, H.H. Lin, W. P. Chuang, C.C. Huang, J.K. Yeh, C.Y. Chu, M.Y. Ho, C.Y. Huang, Y.W. Chen, W. C. Yang, T.H. Lin, Y.W. Wu, Effectiveness and safety of bempedoic acid in Taiwanese patients with hypercholesterolemia: a pragmatic phase 4 study (CLEAR Taiwan Study), J. Am. Heart Assoc. 15 (10) (2026) e049917.
[65] M. Kinoshita, K. Yokote, H. Arai, M. Iida, Y. Ishigaki, S. Ishibashi, S. Umemoto, G. Egusa, H. Ohmura, T. Okamura, S. Kihara, S. Koba, I. Saito, T. Shoji, H. Daida, K. Tsukamoto, J. Deguchi, S. Dohi, K. Dobashi, H. Hamaguchi, M. Hara, T. Hiro, S. Biro, Y. Fujioka, C. Maruyama, Y. Miyamoto, Y. Murakami, M. Yokode, H. Yoshida, H. Rakugi, A. Wakatsuki, S. Yamashita, Committee for E, Clinical Management of A. Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017, J. Atheroscler. Thromb. 25 (9) (2018) 846–984.
[66] D. Masuda, K. Kajinami, N. Sakayoshi, D. Yokota, M. Nagamine, Y. Morikawa-Isogai, S. Yamashita, Long-term safety and efficacy of bempedoic acid in Japanese patients with hypercholesterolemia: the CLEAR-J LONG, J. Atheroscler. Thromb. 33 (4) (2026) 449–469.
[67] C. Pavanello, G. Cincotto, G.G. Mombelli, S. Castiglione, C. Santolamazza, L. Calabresi, C.R. Sirtori, A. Alberti, Clinical implementation of bempedoic acid in blood lipid management: real-world data from an Italian lipid clinic, J. Clin. Lipidol. 19 (6) (2025) 1628–1636.
[68] R.T. White, B.O. Ansong, K. Cowart, Bempedoic acid vs ezetimibe added to statin therapy: Cardiovascular outcomes in the real-world-The BEYOND-REAL Study, J. Clin. Lipidol. 20 (5) (2026) 1023–1029.
[69] J.L. Katzmann, K.K. Ray, B. Lee, C. Becker, K. Articus, A.L. Catapano, U. Laufs, Oral triple combination lipid-lowering therapy and LDL cholesterol goal attainment: a simulation using the SANTORINI study cohort, Eur. J. Prev. Cardiol. (2025).
[70] A. Faggiano, A. Maloberti, M. Ambrosetti, F. Giallauria, G. Mureddu, E. Venturini, M. Ruzzolini, F. Maranta, M. Vatri, L. Zadre, S. Carugo, M. Ruscica, F. Fattirolli, P. Faggiano, From clinical inertia to therapeutic optimization in patients with atherosclerotic cardiovascular disease: a Monte Carlo simulation within the ITACARE-P registry, J. Clin. Lipidol. 20 (1) (2026) 21–30.
[71] S. Raposeiras-Roubin, E. Abu Assi, C. Jimenez Mendez, E. Minguez de la Guia, J. A. Perez Rivera, M. Marcos Mangas, A. Ayesta, A. Uribarri, P. Jorge Perez, P. J. Antunez Muinos, C. Bonanad Lozano, A. Carrasquer, A. Viana-Tejedor, P. Dominguez Erquicia, A. Villar Ruiz, M. Lopez Vazquez, L. Aguilar Iglesias, A. Alen Andremar, M. Vidal Burdeus, M.M. Martin Cabeza, M.C. Gonzalez Cambeiro, D. Bompart, J.C. Gomez Polo, M.T. Garcia Garcia, A. Merino Merino, J. Rozado, J.A. Panera de la Mano, F. Salmeron Martinez, E. Sanchez Corral, I. Santos Sanchez, A.V. Hernandez-Martos, A. Antelo Abejon, A. Iniguez Romo, M. Corbi-Pascual, A. Ariza-Sole, Triple versus dual lipid-lowering therapy in acute coronary syndrome: the ES-BempedACS Randomized Clinical Trial, Circulation 153 (3) (2026) 140–149.
[72] S.B. Jadhav, R.L. Crass, S. Chapel, M. Kerschnitzki, W.J. Sasiela, M.G. Emery, B. M. Amore, P.H.R. Barrett, G.F. Watts, A.L. Catapano, Pharmacodynamic effect of bempedoic acid and statin combinations: predictions from a dose-response model, Eur. Heart J. Cardiovasc. Pharmacother. 8 (6) (2022) 578–586.
[73] B. Yenilmez, M. Kelly, G.F. Zhang, N. Wetoska, O.R. Ilkayeva, K. Min, L. Rowland, C. DiMarzio, W. He, N. Raymond, L. Lifshitz, M. Pan, X. Han, J. Xie, R.H. Friedline, J.K. Kim, G. Gao, M.A. Herman, C.B. Newgard, M.P. Czech, Paradoxical activation of transcription factor SREBP1c and de novo lipogenesis by hepatocyte-selective ATP-citrate lyase depletion in obese mice, J. Biol. Chem. 298 (10) (2022) 102401.
[74] J.Y. Liu, R.S. Kuna, L.V. Pinheiro, P.T.T. Nguyen, J.E. Welles, J.M. Drummond, N. Murali, P.V. Sharma, J.G. Supplee, M. Shiue, S. Zhao, A.T. Farria, A. Kumar, M.

L. Ruchhoeft, C. Demetriadou, D.S. Kantner, A. Chatoff, E. Megill, P.M. Titchenell, N.W. Snyder, C.M. Metallo, K.E. Wellen, Bempedoic acid suppresses diet-induced hepatic steatosis independently of ATP-citrate lyase, Cell. Metab. 37 (1) (2025) 239–254, e237.
[75] F. Di Pastena, J. Gautam, J.S.V. Lally, R. Fayyazi, E. Grasset, D. Bhattacharya, G. Fidelito, E. Ahmadi, L.K. Townsend, B. Batchuluun, D.C. Oniciu, S. Heaton, R. S. Newton, T. Tsakiridis, E.E. Tsakiridis, S. Banskota, P. Deo, F. Briand, K. Hall, E. Lee, V. Muralidharan, M.J. Watt, S.L. Friedman, D. Wang, G.R. Steinberg, Dual inhibition of ACLY and ACSS2 by EVT0185 reduces steatosis, hepatic stellate cell activation, and fibrosis in mouse models of MASH, Cell. Metab. 38 (1) (2026) 33–49, e10.
[76] I. Sakuma, R.C. Gaspar, H.N. Morgan, J. Zheng, A.R. Nasiri, S. Dufour, M. Kahn, M. T. Guerra, Y. Taki, Y. Kawashima, D. Yimlamai, M. Perelis, D.F. Vatner, K. F. Petersen, V.T. Samuel, T. Tanaka, G.I. Shulman, CIDEB and CGI-58 differentially regulate liver lipid-droplet cholesterol to modulate metabolic dysfunction-associated steatohepatitis severity, Cell. Rep. 45 (6) (2026) 117369.
[77] A.P. Beigneux, C. Kosinski, B. Gavino, J.D. Horton, W.C. Skarnes, S.G. Young, ATP-citrate lyase deficiency in the mouse, J. Biol. Chem. 279 (10) (2004) 9557–9564.
[78] Q. Wang, S. Li, L. Jiang, Y. Zhou, Z. Li, M. Shao, W. Li, Y. Liu, Deficiency in hepatic ATP-citrate lyase affects VLDL-triglyceride mobilization and liver fatty acid composition in mice, J. Lipid Res. 51 (9) (2010) 2516–2526.
[79] L. Guo, Y.Y. Guo, B.Y. Li, W.Q. Peng, X.X. Chang, X. Gao, Q.Q. Tang, Enhanced acetylation of ATP-citrate lyase promotes the progression of nonalcoholic fatty liver disease, J. Biol. Chem. 294 (31) (2019) 11805–11816.
[80] D. Gill, M.J. Dib, R. Gill, S.R. Bornstein, S. Burgess, A.L. Birkenfeld, Effects of ACLY inhibition on body weight distribution: a drug target mendelian randomization study, Genes (Basel) 15 (8) (2024).
[81] Z. Chen, R.D. Triatin, L. Luo, H. Snieder, A.F. Schmidt, M. Ditmarsch, J.J. P. Kastelein, R.P.F. Dullaart, J.A. Kuivenhoven, C.H.L. Thio, Drug targets for lipid modification and risk of type 2 diabetes: a cis-Mendelian randomization study, Cardiovasc. Diabetol. (2026).
[82] B.A. Ference, K.K. Ray, A.L. Catapano, T.B. Ference, S. Burgess, D.R. Neff, C. Oliver-Williams, A.M. Wood, A.S. Butterworth, E. Di Angelantonio, J. Danesh, J. J.P. Kastelein, S.J. Nicholls, Mendelian randomization study of ACLY and cardiovascular disease, N. Engl. J. Med. 380 (11) (2019) 1033–1042.
[83] J.L. Ciofani, D. Han, K. Rao, D. Gill, B. Woolf, K. Rahimi, U.K. Allahwala, R. Bhindi, Lipid-lowering therapies for aortic stenosis: a drug-target Mendelian randomization study, Eur. Heart J. Cardiovasc. Pharmacother. 11 (2) (2025) 136–142.
[84] S. Zhao, A. Torres, R.A. Henry, S. Trefely, M. Wallace, J.V. Lee, A. Carrer, A. Sengupta, S.L. Campbell, Y.M. Kuo, A.J. Frey, N. Meurs, J.M. Viola, I.A. Blair, A. M. Weljie, C.M. Metallo, N.W. Snyder, A.J. Andrews, K.E. Wellen, ATP-citrate lyase controls a glucose-to-acetate metabolic switch, Cell. Rep. 17 (4) (2016) 1037–1052.
[85] M.P. Lazaropoulos, A.A. Gibb, D.J. Chapski, A.A. Nair, A.N. Reiter, R. Roy, D. M. Eaton, K.C. Bedi Jr., K.B. Margulies, K.E. Wellen, C. Estaras, T.M. Vondriska, J. W. Elrod, Nuclear ATP-citrate lyase regulates chromatin-dependent activation and maintenance of the myofibroblast gene program, Nat. Cardiovasc. Res. 3 (7) (2024) 869–882.
[86] P. Icard, Z. Wu, L. Fournel, A. Coquerel, H. Lincet, M. Alifano, ATP citrate lyase: A central metabolic enzyme in cancer, Cancer Lett. 471 (2020) 125–134.
[87] W. Zheng, L. Tasselli, T.M. Li, K.F. Chua, Mammalian SIRT6 represses invasive cancer cell phenotypes through ATP Citrate Lyase (ACLY)-dependent histone acetylation, Genes (Basel) 12 (9) (2021).
[88] A. Garcia-Bautista, A. Cenigaonandia-Campillo, A. Rio-Vilarino, L. Sanz-Criado, M. Selva-Gimenez, R. Perez-Antolin, A. Cebrian, L. Garcia-Garcia, M.J. Fernandez-Acenero, N. Banos-Herraiz, L. Mozas-Vivar, E. Nunez-Delicado, J. Garcia-Foncillas, O. Aguilera, Metabolic regulation of histone acetylation by ACLY supports MDR1 expression in colorectal cancer and highlights a targetable vulnerability, Neoplasia 77 (2026) 101314.
[89] Y. Zhang, X. Shen, Y. Shen, C. Wang, C. Yu, J. Han, S. Cao, L. Qian, M. Ma, S. Huang, W. Wen, M. Yin, Q.Y. Lei, Cytosolic acetyl-coenzyme A is a signalling metabolite to control mitophagy, Nature 649 (8098) (2026) 1022–1031.
[90] P.G. Kim, C.B. Hergott, A.P. Miller, A. Deik, M. Boileau, K. Bullock, K.A. Pierce, A. H. Choy, W. Shin, M. McConkey, J. Loke, B.A. Ryback, M.N. Trinh, J.C. Rutter, H. Yue, H. Yoon, P. Park, S.S. Roy Burman, M.G. Vander Heiden, E.S. Fischer, S. A. Armstrong, C. Clish, B.L. Ebert, Metabolic control of innate immune activation in TET2-mutant clonal hematopoiesis, Cell. Chem. Biol. 33 (2) (2026) 183–197, e189.
[91] T. Wartewig, J. Daniels, M. Schulz, E. Hameister, A. Joshi, J. Park, E. Morrish, A. V. Venkatasubramani, F.M. Cernilogar, F.H.A. van Heijster, C. Hundshammer, H. Schneider, F. Konstantinidis, J.V. Gabler, C. Klement, H. Kurniawan, C. Law, Y. Lee, S. Choi, J. Guitart, I. Forne, J. Giustinani, M. Muschen, S. Jain, D. M. Weinstock, R. Rad, N. Ortonne, F. Schilling, G. Schotta, A. Imhof, D. Brenner, J. Choi, J. Ruland, PD-1 instructs a tumor-suppressive metabolic program that restricts glycolysis and restrains AP-1 activity in T cell lymphoma, Nat. Cancer 4 (10) (2023) 1508–1525.
[92] Y. Wang, K. Su, C. Wang, T. Deng, X. Liu, S. Sun, Y. Jiang, C. Zhang, B. Xing, X. Du, Chemotherapy-induced acetylation of ACLY by NAT10 promotes its nuclear accumulation and acetyl-CoA production to drive chemoresistance in hepatocellular carcinoma, Cell. Death Dis. 15 (7) (2024) 545.
[93] A. Santarsiero, P. Convertini, S. Todisco, C.L. Pierri, A. De Grassi, N.C. Williams, D. Iacobazzi, G. De Stefano, L.A.J. O'Neill, V. Infantino, ACLY nuclear translocation in human macrophages drives proinflammatory gene expression by NF-kappaB acetylation, Cells 10 (11) (2021).
[94] P. Convertini, A. Santarsiero, S. Todisco, M. Gilio, D. Palazzo, I. Pappalardo, D. Iacobazzi, M. Frontuto, V. Infantino, ACLY as a modulator of liver cell functions and its role in metabolic dysfunction-associated steatohepatitis, J. Transl. Med. 21 (1) (2023) 568.
[95] J.T. Noe, B.E. Rendon, A.E. Geller, L.R. Conroy, S.M. Morrissey, L.E.A. Young, R. C. Bruntz, E.J. Kim, A. Wise-Mitchell, M. Barbosa de Souza Rizzo, E.R. Relich, B. V. Baby, L.A. Johnson, H.C. Affronti, K.M. McMasters, B.F. Clem, M.S. Gentry, J. Yan, K.E. Wellen, R.C. Sun, R.A. Mitchell, Lactate supports a metabolic-epigenetic link in macrophage polarization, Sci. Adv. 7 (46) (2021) eabi8602.
[96] W. Xiang, H. Lv, F. Xing, X. Sun, Y. Ma, L. Wu, G. Lv, Q. Zong, L. Wang, Z. Wu, Q. Feng, W. Yang, H. Wang, Inhibition of ACLY overcomes cancer immunotherapy resistance via polyunsaturated fatty acids peroxidation and cGAS-STING activation, Sci. Adv. 9 (49) (2023) eadi2465.