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Beyond statins: New pharmacological targets to decrease LDL-cholesterol and cardiovascular events

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ABSTRACT

The pharmacological treatment of dyslipidemia, a major modifiable risk factor for developing atherosclerotic cardiovascular disease (ASCVD), remains a debated and controversial issue, not only in terms of the most appropriate therapeutic range for lipid levels, but also with regard to the optimal strategy and sequence approach (stepwise vs upstream therapy). Current treatment guidelines for the management of dyslipidemia focus on the intensity of low-density lipoprotein cholesterol (LDL-C) reduction, stratified according to risk for developing ASCVD. Beyond statins and ezetimibe, different medications targeting LDL-C have been recently approved by regulatory agencies with potential innovative mechanisms of action, including proprotein convertase subtilisin/kexin type 9 modulators (monoclonal antibodies such as evolocumab and alirocumab; small interfering RNA molecules such as inclisiran), ATP-citrate lyase inhibitors (bempedoic acid), angiopoietin-like 3 inhibitors (evinacumab), and microsomal triglyceride transfer protein inhibitors (lomitapide). An understanding of their pharmacological aspects, benefit-risk profile, including impact on hard cardiovascular endpoints beyond LDL-C reduction, and potential advantages from the patient perspective (e.g., adherence) - the focus of this evidence-based review - is crucial for practitioners across medical specialties to minimize therapeutic inertia and support clinical practice.

Contents

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List of abbreviations

ASCVD	atherosclerotic cardiovascular disease
ACC	American College of Cardiology
AEs	adverse events
AHA	American Heart Association
LDL-C	low-density lipoprotein cholesterol
BA	bempedoic acid
ESC	European Society of Cardiology
EAS	European Atherosclerosis Society
EMA	European Medicines Agency
FDA	Food and Drug Administration
LDLR	low-density lipoprotein cholesterol receptor
mAbs	monoclonal antibodies
MACE	major adverse cardiovascular events
PCSK9	proprotein convertase subtilisin/kexin type 9
RCTs	randomized controlled trials
SAMS	statin-associated muscle symptoms

1. Introduction

The global burden of dyslipidaemias, in terms of prevalence and related mortality, increased substantially in the past three decades, with hypercholesterolemia being the most prevalent form. Importantly, elevated plasma low-density lipoprotein cholesterol (LDL-C) levels are recognized as a major causal factor for developing atherosclerotic cardiovascular disease (ASCVD) in both the developed and the developing world (Pirillo, Casula, Olmastroni, Norata, & Catapano, 2021). The notion of a "cause-effect" relationship between LDL-C lowering and cardiovascular risk reduction carries remarkable implications for clinical practice. In secondary prevention, a meta-analysis by the Cholesterol Treatment Trialists Collaboration (CTTC) demonstrated that a 1 mmol/L (or 39 mg/ dL) LDL-C reduction drove a 12% reduction in all-cause mortality, a 23% reduction in myocardial infarction or coronary death, a 24% reduction in coronary revascularization, and a 17% reduction in non-fatal stroke (Baigent et al., 2005).

While precise goals for LDL-C reduction have been a matter of intense debate, evolving data have demonstrated the benefits of lowering LDL-C well below the commonly recommended 70 mg/dL for patients at high risk or with a history of prior ASCVD (Ference et al., 2017; Silverman et al., 2016). In the wake of this evidence, the 2018 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines identified LDL-C of 70 mg/dL as a threshold for adding non-statin drugs (Grundy et al., 2019), whereas the 2019 European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines even recommended LDL-C <55 mg/dL as a goal for those at very high risk in primary and secondary prevention (Class I recommendation) (Knuuti et al., 2020; Mach et al., 2020). Notably, the importance of lipid management in high-risk groups represents a multidisciplinary issue, and the Endocrine Society Guidelines recommended an LDL-C <55 mg/dL for patients with endocrine disorders and established cardiovascular disease or multiple risk factors (Newman et al., 2020).

By virtue of their consolidated excellent benefit-risk profile (Collins et al., 2016), statins are worldwide recommended as first-line pharmacological approach in both primary and secondary cardiovascular prevention. Lovastatin was the first statin approved for clinical use by the Food and Drug Administration (FDA) on September 1st, 1987. Since then, different statins have been introduced in clinical practice, with slight differences in terms of chemical structure, biological properties, pharmacological (pharmacokinetics, intensity in the ability to cause LDL-C reduction) and clinical features (safety and potential for drug interactions) (Corsini et al., 1999; Ferri & Corsini, 2020; Schachter, 2005).

Unfortunately, statin therapy remains suboptimal due to substantial clinical inertia. Therefore, in the past decade, the therapeutic panorama of lipid-lowering drugs has expanded rapidly and substantially to address the unmet need of residual cardiovascular risk and tackle barriers precluding the achievement of LDL-C goals in clinical practice (Ferraro et al., 2022) Fig. 1. Clinicians are facing a challenging and stimulating scenario in which different evidence-based medications can effectively lower LDL-C to counteract the development of ASCVD with potentially innovative mechanisms of action, including proprotein convertase subtilisin/kexin type 9 (PCSK9) modulators (monoclonal antibodies and small interfering RNA molecules), ATP-citrate lyase inhibitors, angiopoietin-like 3 inhibitors (evinacumab), and microsomal triglyceride transfer protein inhibitors (lomitapide) (Mourikis et al., 2020) Fig. 2.

This evidence-based review is devoted to the clinical pharmacology and benefit-risk assessment of these non-statin drugs, including the impact on hard cardiovascular endpoints (i.e., beyond LDL-C reduction), and potential advantages from the patient perspective (i.e., adherence). Except for ezetimibe, older drugs causing mild LDL-C reduction (15-20%) such as bile acid sequestrants, niacin, and fibrates are not covered. Likewise, the role of apheresis and ileal bypass, as well as a detailed evaluation of other non-pharmacological strategies, including the role of nutraceuticals in the optimization of lipid-lowering treatment, is beyond the aim of this review, and the reader should refer to dedicated state-of-the-art reviews and position papers (Banach et al., 2018; Casula, Catapano, & Magni, 2022; Cicero et al., 2017). We offer this pharmacological update to general practitioners and clinicians across different specialties, in order to minimize therapeutic inertia and inform evidence-based clinical practice. Therefore, a brief summary on the multifaceted notion of statin intolerance is anticipated (Drexel et al., 2020). A critical insight into the evolving therapeutic paradigm (stepwise vs upstream therapy) is also provided .

2. Statin intolerance and *drucebo* effect: the need to get it right

Although efficacy and safety of statin therapy are well established in different populations, subgroups and regimens (Baigent et al., 2005; Cholesterol Treatment Trialists' Collaboration, 2019; Cholesterol Treatment Trialists' (CTT) Collaboration et al., 2010; Cholesterol Treatment Trialists' (CTT) Collaborators et al., 2012; Collins et al., 2016), statin intolerance limits their use, negatively impacting adherence and cardiovascular benefits of this treatment (Mach et al., 2020). According to the International Lipid Expert Panel, statin intolerance is an inability to tolerate a dose of statin required to sufficiently reduce an individual's cardiovascular risk (Banach et al., 2015), or more rigorously is defined as the inability to tolerate at least two statins (Guyton et al., 2014), namely switching between ≥3 types of statins within 1 year (Serban et al., 2017).

Several adverse effects have been attributed to statins, with muscle symptoms being the most common (Stroes et al., 2015). Although muscle symptoms are real, some can be attributed to the so-called *drugcebo* effect, which results in the difference in the frequency or intensity of symptoms between blinded and open-label uses of a drug (Penson & Banach, 2021). Caution is needed before attributing muscle symptoms to statin therapy, and further investigation of the underlying cause is warranted.

Several reports have indicated the potential clinical significance of plain myalgia. Although data based on observational studies and registries indicated an incidence of statin-associated muscle symptoms (SAMS) between 17% and 30%, randomized controlled trials (RCTs) suggest a much lower rate (4.9%) (Ruscica, Ferri, Banach, Sirtori, & Corsini, 2023). This is confirmed by a recent meta-analysis and an observational retrospective study, which estimated an overall prevalence of 9.1% for statin intolerance (similar using different international definitions, reaching 17% when analyzing only cohort studies) (Bytyçi et al., 2022; Casula et al., 2021).

Perhaps the Effects of Statins on Muscle Performance (STOMP) study provides the best evidence to date on the true incidence of SAMS (Parker et al., 2013). STOMP is the only randomized, double-blind, placebo-controlled study specifically designed to evaluate the effects

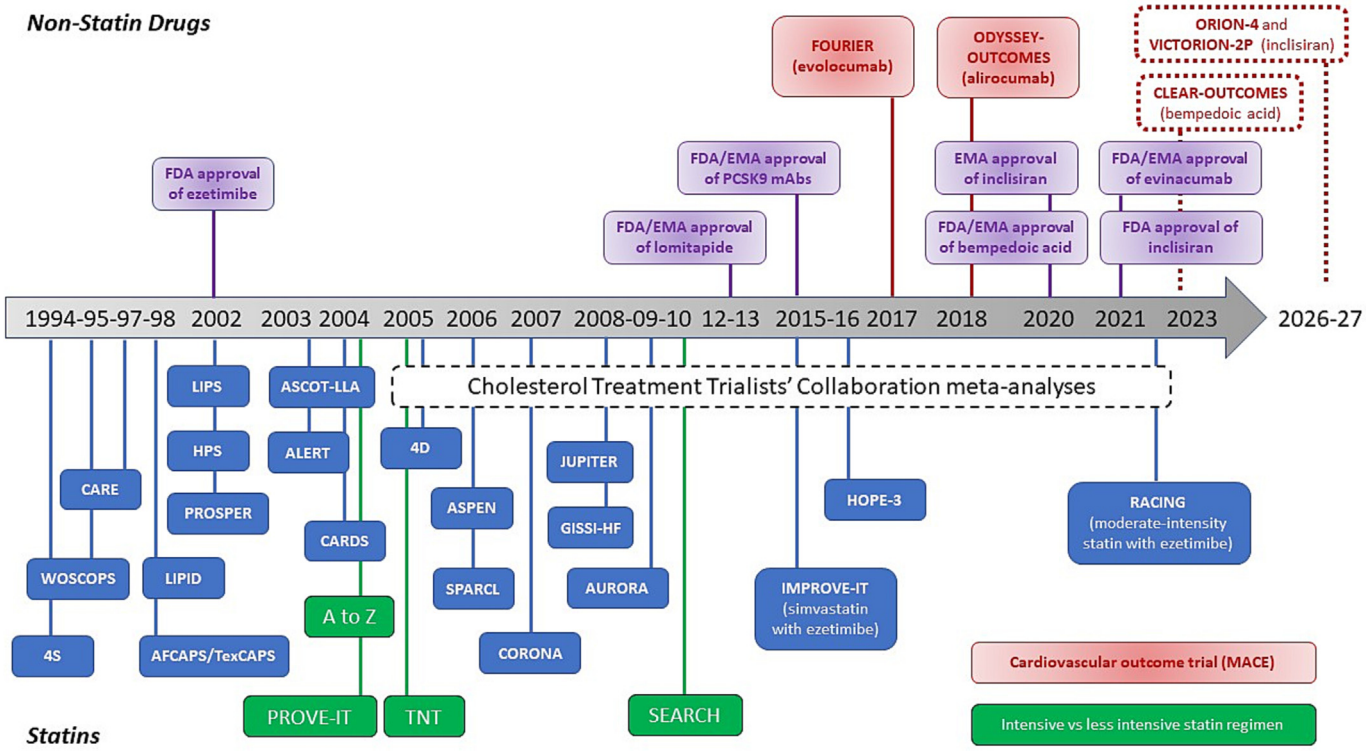

Fig. 1. Timeline and milestones of pharmacological strategies for LDL-C reduction.
EMA: European Medicines Agency; FDA: Food and Drug Administration; MACE: Major Adverse Cardiovascular Events.

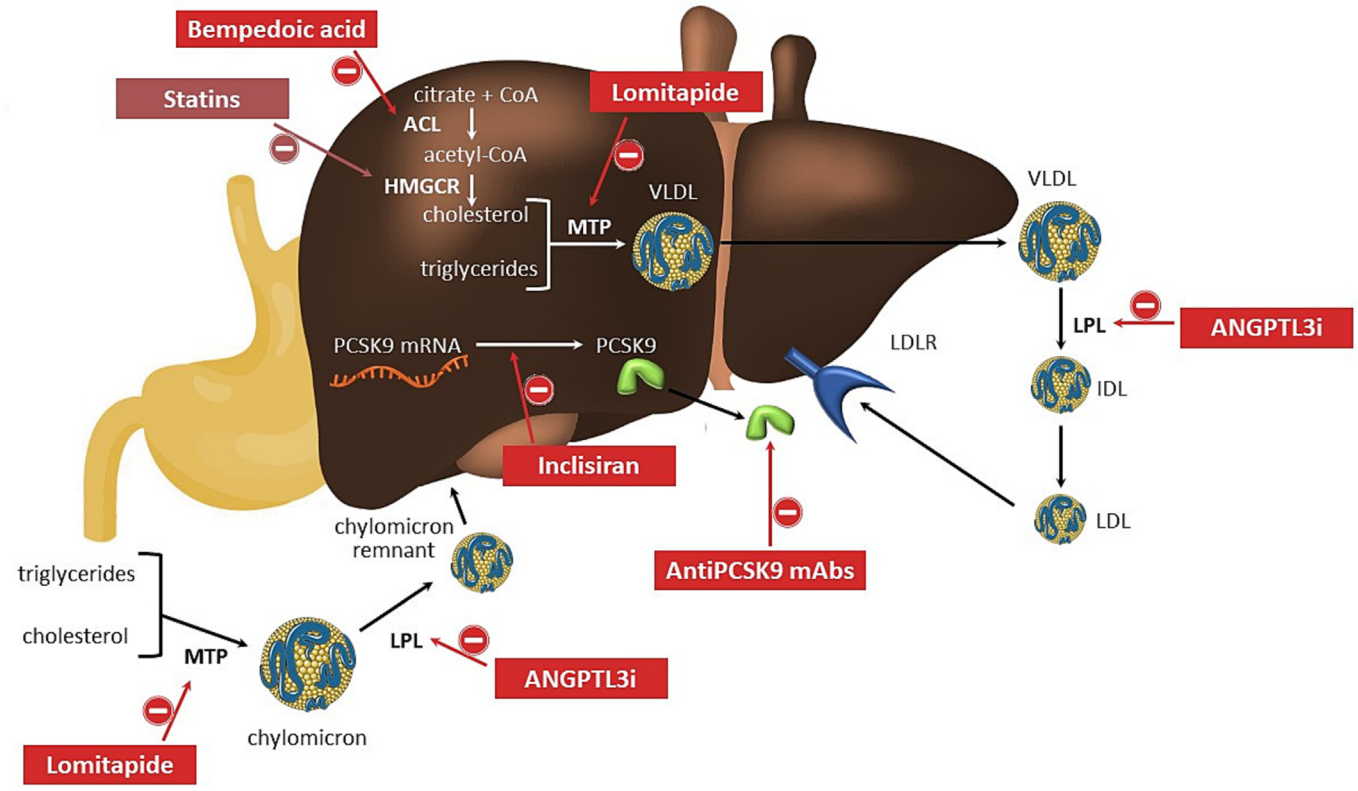

Fig. 2. Targets and mechanisms of action of non-statin therapies for LDL-C lowering.
ACL: adenosine triphosphate-citrate lyase; ANGPTL3: angiopoietin-like 3; HMGCR: HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; MTP: microsomal triglyceride transfer protein; LDL-C: LDL cholesterol; LDLR: LDL receptor; LPL: lipoprotein lipase; PCSK9: Proprotein convertase subtilisin/kexin type 9.

of treatment with a statin (atorvastatin 80 mg daily) on skeletal muscle in 420 statin-naïve patients treated for 6 months. Importantly, STOMP incorporated predefined criteria for statin myalgia, which included onset of symptoms during statin treatment which persisted for 2 weeks, resolved within 2 weeks of stopping treatment and reappeared within 4 weeks of restarting treatment. Overall, 9.4% of patients treated with atorvastatin and 4.6% on placebo met the criteria of statin myalgia ($p=0.054$). This suggests that true SAMS might affect <5% of patients in routine practice. Of note, the StatinWISE and SAMSON n-of-1 trials documented the feasibility to successfully restart treatment with a statin in a large proportion of participants (Herrett et al., 2021; Krishnamurthy, Bradley, Ascunce, & Kim, 2022).

Altogether, the management of SAMS is a key in the effective treatment of patients with cardiovascular disease, through achievement of maximum tolerated statin dosing and other practical aspects such as combination therapy with non-statin drugs (Banach, Cannon, et al., 2022).

3. Non-statin drugs

This section is devoted to the critical analysis of novel drugs beyond statins, focusing on clinical pharmacology and benefit-risk assessment (cardiovascular effect, safety and prescribing aspects). A synopsis of key pharmacological features is provided in Table 1 and Fig. 2.

The beginning of the era of non-statin drugs could be identified with the 2002 FDA approval of ezetimibe, a putative inhibitor of the Niemann–Pick transporter C 1 like 1 on enterocytes Fig. 1. This mechanism selectively inhibits intestinal absorption of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. Ezetimibe possesses desirable pharmacological properties that may contribute to its favorable safety and tolerability profile (myalgia and/or increased transaminases 0.1–1%; myopathy <0.1%). There are no clinically significant effects of age, sex or race on ezetimibe pharmacokinetics and no dosage adjustment is necessary in patients with mild hepatic impairment or mild-to-severe renal impairment. By virtue of its extensive glucuronidation and apparent negligible affinity for hepatic isoenzymes and transporters, ezetimibe is relatively unsusceptible to metabolic drug-drug interactions, as evidenced by the lack of clinically relevant interactions with statins (Kosoglou et al., 2005). At the recommended dose of 10 mg/day, ezetimibe had been shown to lower LDL-C concentrations by approximately 18% (Pandor et al., 2009), with incremental 25% LDL-C reduction in combination with statins (Mach et al., 2020).

The 2015 was a remarkable year; first, monoclonal antibodies (mAbs) against PCSK9 were approved by the FDA and the European Medicines Agency (EMA); second, the IMPROVE-IT landmark study was the first clinical trial to show a benefit of adding ezetimibe to statin therapy (an approximately 24% incremental reduction in LDL-C vs simvastatin alone, with 2% absolute risk reduction of the composite cardiovascular endpoint) in subjects with recent myocardial infarction (Cannon et al., 2015). These findings, while strengthening the LDL hypothesis, open new avenues on the era of non-statin drugs (and relevant combination with statins) by suggesting that all reductions in LDL-C levels, regardless of mechanism, are of equivalent benefit.

In subsequent years, research has progressed in the study of alternative LDL-lowering options to statins, leading to the availability of inclisiran, a PCSK9 inhibitor working by RNA interference, and bempedoic acid, the most recent oral lipid-lowering drug.

3.1. Bempedoic acid

3.1.1. Clinical pharmacology

Bempedoic acid (BA) is a first-in-class competitive inhibitor of adenosine triphosphate (ATP)-citrate lyase (ACL), thus acting upstream as compared to statins (Ballantyne et al., 2021). The oral prodrug is converted to the bempedoyl CoA active form by the very long-chain acyl-CoA synthetase-1 (ACSVL1), an enzyme expressed mainly in the liver and kidney, but not in the skeletal muscle or other tissues (Pinkosky et al., 2016). ACL is a cytosolic enzyme catalysing the cleavage of mitochondrial-derived citrate to cytosolic acetyl-CoA and oxaloacetate; acetyl-CoA, a precursor of the mevalonate pathway of cholesterol biosynthesis, is the fundamental building block for both *de novo* cholesterol and fatty acid synthesis (Ruscica, Banach, Sahebkar, Corsini, & Sirtori, 2019). Therefore, the blockade of ACL results in decreased synthesis of LDL-C in the liver, with upregulation of hepatic LDL-R, thus increasing LDL-C clearance from the blood.

In addition, based on *in vitro*/*in vivo* studies, BA directly activates AMP-activated protein kinase (AMPK), which in turn downregulates glucose-6-phosphatase and phosphoenolpyruvate carboxykinase. This mechanism may lower liver fatty acid while reducing glucose intolerance, liver steatosis, and ballooning, without increasing circulating triglycerides (Morrow et al., 2022). Moreover, it downregulates pro-inflammatory pathways in immune cells and other tissues, thus leading to decreased cytokine, chemokine, and adhesion molecule synthesis. The resulting anti-inflammatory effect may have benefits in atherosclerosis, obesity, diabetes and even cancer, although the clinical relevance of possible AMPK stimulation in humans is still unclear (Biolo et al., 2022).

Food has no effect on the oral bioavailability of BA, and its pharmacokinetics (PK) is not affected by age, sex, race, or weight, with no time-dependent changes in the pharmacokinetic profile (Cicero, Fogacci, & Cincione, 2021). Although slight increases were observed in subjects with mild to moderate renal and hepatic impairment (with no data in severe stages), the observed differences were not considered clinically relevant (Markham, 2020). It is approximately 99% protein bound in plasma, with a volume of distribution of 18 L. Based on *in vitro* studies, BA glucuronide is a substrate for and a weak inhibitor of the organic anion transporter (OAT) 3, and also weakly inhibits OAT2. Co-administration of simvastatin 20 mg with BA 240 mg, or simvastatin 40 mg with BA 180 mg, resulted in approximately 2- and 1.5-fold increase of the area under the curve (AUC) and C_{max} of simvastatin, with an unclear mechanism (possibly ascribed to the inhibition of the OAT polypeptide 1B1). Conversely, the observed changes in the PK of ezetimibe when given concomitantly with BA are not clinically meaningful and do not affect dosing recommendations (Ballantyne et al., 2020). The drug is primarily eliminated via metabolism of the acyl glucuronide (minimally by cytochrome CYP-450), with approximately 70% and 30% of the total dose recovered in urine and faeces, respectively, after oral administration of a single 240 mg dose (unchanged <5%).

3.1.2. Cardiovascular benefit

The safety and efficacy of the long-term use of BA have been addressed in the CLEAR (Cholesterol Lowering via BEmpedoic Acid, an ACL-inhibiting Regimen) program comprising four phase 3 trials: CLEAR Tranquility (Ballantyne et al., 2018), CLEAR Harmony (Ray et al., 2019), CLEAR Wisdom (Goldberg et al., 2019), and CLEAR Serenity (Laufs et al., 2019). Notwithstanding differences in the population enrolled across trials, including LDL-C levels ranging from 103.2 to 157.6 mg/dL and documented statin intolerance, BA showed consistent superiority over placebo, with modest by sustained effect in reducing LDL-C through 24 to 52 weeks of follow-up, as well as up to 2.5 years in the open-label extension of the CLEAR Harmony study (Ballantyne et al., 2022). According to a systematic review with meta-analysis of 10 phase II/III RCTs, BA significantly reduced total cholesterol (mean differences [MD] −14.94%; 95% CI −17.31%, −12.57%), non-HDL-C (MD −18.17%; 95% CI −21.14%, −15.19%), LDL-C (MD −22.94%; 95% CI −26.63%, −19.25%), apolipoprotein B (MD −15.18%; 95% CI −17.41%, −12.95%), HDL-C (MD −5.83%; 95% CI −6.14%, −5.52%), without significant changes of triglyceride level (MD −1.51%; 95% CI −3.75%, 0.74%) (Cicero, Fogacci, et al., 2020).

Although large variability in LDL-C reduction should be noted (Patti et al., 2022), some key findings can be identified. The extent of lipid-

Table 1
Comparative pharmacological aspects of newer non-statin drugs (ezetimibe excluded). ▼ Under additional monitoring. EC: under exceptional circumstances. Data were obtained from summary of product characteristics (EMA) and prescribing information (FDA).

Feature	Bempedoic acid▼	Lomitapide (EC)▼	Evolocumab	Alirocumab	Inclisiran ▼	Evinacumab (EC)▼
Pharmacological class	small molecule	small molecule	Fully human mAb	Fully human mAb	SiRNA	Fully human mAb
Marketing Approval	2020 (FDA, EMA)	2013 (EMA) 2012 (FDA)	2015 (FDA, EMA)	2015 (FDA, EMA)	2020 (EMA)	2021 (FDA, EMA)
Therapeutic Indication	Primary hypercholesterolemia or mixed dyslipidemia (EMA); HeFH; ASCVD (FDA only)	HoFH	Primary hypercholesterolaemia and mixed dyslipidaemia; HeFH; ASCVD; HoFH (FDA only)	Primary hypercholesterolaemia and mixed dyslipidaemia; HeFH; ASCVD; HoFH (FDA only)	Primary hypercholesterolemia or mixed dyslipidemia; HeFH; ASCVD (FDA only)	HoFH
Posology	180 mg/day per os with or without food	5 mg/day per os as starting dose, with titration to max 60 mg/day (empty stomach)	Subcutaneous injection (140 mg every 2 weeks or 420 mg once monthly) over 9 minutes (single-use on-body infusor with prefilled cartridge), or by 3 injections consecutively within 30 minutes (single-use prefilled autoinjector or syringe)	Subcutaneous injection (75–150 mg once every 2 weeks or 300 mg once every 4 weeks)	Subcutaneous injection (284 mg every 3–6 months)	Intravenous infusion over 60 minutes (15 mg/kg every 4 weeks)
Target	ACL	MTP	PCSK9 (increased hepatic production)	PCSK9 (increased hepatic production)	PCSK9 (reduced hepatic production)	ANGPTL3
Pharmacodynamics	Inhibition of ACL results in decreased cholesterol synthesis in the liver, with upregulation of LDLR, nadir at week 4 in LDL-C reduction. Suppression of hepatic fatty acid biosynthesis	Inhibition of MTP reduces lipoprotein secretion and circulating cholesterol and triglycerides, apparent by day 14, nadir at week 18	Inhibition of circulating PCSK9 from binding to the LDLR (maximum suppression of circulating unbound PCSK9 within 4 hours), nadir by 14–21 days, with equivalent-sustained LDL-C reduction over 112 weeks for the two regimens	Inhibition of circulating PCSK9 from binding to the LDLR (maximum suppression of PCSK9 within 4–8 hours following the administration of 75 or 150 mg)	Inhibition of hepatic PCSK9, with increase in LDLR recycling and expression. LDL reduction apparent by day 14 with peak reduction at 60 days for single-dose and 150 days for two-dose regimens	Inhibition of lipoprotein lipase and endothelial lipase, with LDL-C reduction independently of LDLR, apparent by day 14
LDL-C reduction as monotherapy (change from baseline)	15–23.5%	~45% (RCT)–60% (OBS)	57–72%	47–61%	40–51%	47%
Cardiovascular benefit (MACE)	YES (RCT)	YES (OBS)	YES (RCT)	YES (RCT)	Not determined	Not determined
Bioavailability	Not measurable	7% (strict low-fat diet)	72%	85%	~40% (estimated from animal studies)	Unknown
Metabolism	Glucuronide (UGT2B7 mediated); pro-drug (activated by ACSVL1, mainly in the liver)	CYP3A4 substrate and inhibitor	Unlikely hepatic metabolic mechanisms	Unlikely hepatic metabolic mechanisms	Nucleases (no substrate of CYPs or transporters)	No metabolism studies performed
Elimination	Urine and feces (5% unchanged)	Urine and feces (93%)	Non-saturable proteolytic pathway	Non-saturable proteolytic pathway	Kidney (16%)	Non-saturable proteolytic pathway
$t_{1/2}$	15–24 h	29–39 h	11–17 days	17–20 days	9 h	Not constant, is a function of evinacumab concentrations (19 weeks to reduce below limit of quantification)
Use in pregnancy	Contraindicated	Contraindicated	It is preferable to avoid use (no reproductive toxicity from animal studies)	Not recommended (maternal toxicity noted in rats)	It is preferable to avoid use	Not recommended (use contraception for at least 5 months after last dose)
Use in renal impairment	No dose adjustment in mild or moderate renal impairment	Max 40 mg/day in end-stage renal disease	No dose adjustment (no observed differences in PK-PD from RCTs)	No dose adjustment in mild to moderate renal impairment (no studies in severe impairment)	No dose adjustments in mild, moderate or severe renal impairment or end-stage renal disease	No dose adjustment
Use in liver impairment	No dose adjustment in mild or moderate hepatic impairment	Contraindicated (moderate or severe hepatic impairment); max 40 mg/day in mild hepatic impairment	No dose adjustment in mild to moderate hepatic impairment (no studies in severe impairment)	No dose adjustment in mild to moderate hepatic impairment (limited data in severe impairment)	No dose adjustment in mild or moderate hepatic impairment	No dose adjustment

(continued on next page)

Table 1 (*continued*)

Feature	Bempedoic acid▼	Lomitapide (EC)▼	Evolocumab	Alirocumab	Inclisiran ▼	Evinacumab (EC)▼
Main safety issues and monitoring	Hyperuricemia, increased liver transaminases (common), tendon rupture, myalgia and muscle spams (rare/unknown)	Gastrointestinal disorders (very common), hepatotoxicity (common), hepatic steatosis (w/o insulin resistance). Liver monitoring prior initiating and before each dose escalation or monthly in the first year (EMA)	Hypersensitivity (including angioedema; rare), injection site reactions, musculoskeletal disorders, upper respiratory tract infections (including nasopharyngitis (common), glycemia impairment (but not diabetes; rare/unknown), neurocognitive effects (rare/unknown)	Hypersensitivity (including angioedema; rare), injection site reactions, upper respiratory tract infections (common), glycemia impairment (but not diabetes; rare/unknown), neurocognitive effects (rare/unknown)	Injection site reactions (common), increased liver transaminases (rare/unknown)	Injection site reactions (common), serious hypersensitivity reactions (including anaphylaxis; uncommon), nasopharyngitis (very common), musculoskeletal, gastrointestinal disorders and dizziness (common)
Drug-drug Interactions	OATP1B1/3, OAT2, OAT3 transporter mediated. Simvastatin (2-fold-increase, with 50% dose reduction)	CYP3A4 inhibitors (contraindicated; 27-fold increase in lomitapide AUC). Warfarin (1.26-fold INR increase) Statins (50% dose reduction of simvastatin). Fat-soluble vitamins malabsorption and BAS (4-h interval)	Not expected from PK. In patients with coadministered statins, 20% increase in the clearance of evolocumab was observed (no impact on evolocumab PD and no dose adjustment of statins)	Not expected from PK. In patients with coadministered statins, 4% reduction in alirocumab exposure was observed (no impact on alirocumab PD and no dose adjustment of statins)	Not expected from PK. Long-term safety is missing	Not expected from PK. Long-term safety is missing
Ecotoxicity/environmental risk assessment (ERA)	No concern	No concern	No ERA performed (no concern expected)	No ERA performed (no concern expected)	No definite conclusion (phase II assessment is ongoing)	No ERA performed (no concern expected)

ACL: adenosine triphosphate-citrate lyase; ACSVL1: very long-chain acyl-Coa Synthetase 1; ANGPTL3: angiopoietin-like 3; ASCVD: atherosclerotic cardiovascular disease; AUC: area under the curve; BAS: bile acid sequestrants; CYP: cytochrome; EMA: European Medicines Agency; ERA: environmental risk assessment; FDA: Food and Drug Administration; HeFH: heterozygous familial hypercholesterolemia; HoFH: homozygous familial hypercholesterolaemia; INR: international normalized ratio; LDL-C: LDL cholesterol; LDLR: LDL receptor; MACE: major adverse cardiovascular events; MTP: microsomal triglyceride transfer protein; PCSK9: Proprotein convertase subtilisin/kexin type 9; PD: pharmacodynamics; PK: pharmacokinetics; RCT: randomized controlled trials; OBS: observational setting.

lowering suggests an additive effect of BA and ezetimibe due to complementary mechanisms (Ballantyne et al., 2020). Interestingly, 33.7% of patients experienced an LDL-C reduction from baseline of ≥50%. Conversely, the addition of BA to background statin may limit the potential for completely additive pharmacodynamic effect, as anticipated by a dose-response prediction model, which found that adding BA to statin therapy is at least equivalent to or more effective in lowering LDL-C than an increase in a statin dose after initial treatment (Jadhav et al., 2022). In patients already at maximally tolerated statin, the addition of BA may give a smaller contribution, as supported by different pooled analyses. As monotherapy, LDL-C was reduced by 17.8% in patients on statins (24.5% in statin-intolerant individuals), whereas roughly by 38% when given as a fixed-dose combination with ezetimibe as compared to placebo, with similar percentages in patients not receiving statins (26.5% and 39.2%, respectively) (Laufs et al., 2022).

In the evaluation of the ASCVD risk reduction, the lowering activity on high-sensitivity C-reactive protein (hs-CRP) of BA, consistent across all pivotal phase 3 trials (median % change from baseline to week 12 ranging from −18.7% to −32.5%), should not be overlooked (Ruscica, Corsini, Ferri, Banach, & Sirtori, 2020). In fact, hs-CRP is an established prognostic marker of future coronary events, as shown in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial with canakinumab (Ridker et al., 2017), a monoclonal antibody targeting interleukin-1β, and considering statin trials, where clinical benefit appeared to be maximal in the patients with the highest baseline hsCRP levels (Ridker, MacFadyen, Libby, & Glynn, 2010).

Based on expected absolute LDL-C reductions (19.8 to 36.5 mg/dL on average), the corresponding risk reduction of cardiovascular events with BA would theoretically range from 11% to 21% over 5 years (Banach et al., 2020). This impact on major adverse cardiovascular events (MACE) was assessed by the CLEAR Outcomes trial (NCT02993406) in a mixed population of 13,970 statin-intolerant patients (unable or unwilling to take guideline-recommended doses of statins) for whom primary or secondary prevention was clinically indicated. In these patients, who were at high risk for ASCVD (mean LDL-C level at baseline of 139.0 mg/dL, 46% had diabetes, 70% had experienced a previous cardiovascular event), the 21% reduction in LDL-C corresponded to a 13% lower risk of MACE (a four-component composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) as compared to placebo over a median of 3.4 years, without significant effect on death from cardiovascular causes and death from any cause (effects similar to those observed in other trial for PCSK9 inhibitors) (Nissen et al., 2023). This modest absolute reduction in cardiovascular events translates into a number needed to treat of 211 patients per year (Volpe & Patrono, 2023).

3.1.3. Safety aspects

Overall, BA possesses a favorable safety and tolerability profile, with no significant increase of serious adverse events (AEs) from phase II/III RCTs (Cicero, Fogacci, et al., 2020). The most common treatment-emergent AEs in pivotal trials, regardless of causality, were nasopharyngitis, urinary tract infection, and arthralgia, all occurring at a lower frequency as compared to placebo (Banach et al., 2020). BA was not associated with a clinically meaningful increase in the incidence of muscle-related AEs, including myalgia and muscle weakness, as compared to placebo (15.4 vs 11.9 rate per 100 person-years – PY) (Bays et al., 2020). Only muscle spasms (4.4/100 vs 3.0/100 PY) and pain in extremity (3.7/100 vs 2.0/100 PY) were more frequently reported with BA than placebo, also in subjects not taking statins (8.5/100 PY vs 7.4/100 PY; 6.9/100 PY vs 4.2/100 PY, respectively) (Laufs et al., 2022). A slightly higher discontinuation emerged (13.4/100 vs 8.9/100 PY in subjects receiving placebo, respectively), with mild increases (clinically irrelevant) in creatinine (by mean 0.048 mg/dL), and uric acid (by mean 0.82 mg/dL, apparent within 4 weeks of treatment, stable over time, and reversible after drug withdrawal) and

mild reversible decreases in hemoglobin (reductions of ≥2 g/dL in 4.9/100 vs 2.0/100 PY, respectively).

Among AEs of special interest, tendon rupture was found in 0.5% of patients, all occurring in subjects taking moderate- or high-dose statins with one or more risk factors (e.g., fluoroquinolone or systemic corticosteroid use, diabetes, gout, rheumatoid arthritis, renal failure, patients older than 60 years with a history of tendon disorders). Development of gout, a drug-specific side effect likely related to inhibition of renal OAT2 transporter, occurred in 1.4% and 0.4% of patients (incidence of 1.6/100 vs 0.5/100 PY in the BA vs placebo groups), with higher risk in patients with history of gout or high baseline levels of uric acid (Bays et al., 2020; Cicero, Pontremoli, Fogacci, Viazzi, & Borghi, 2020; Laufs et al., 2022). Therefore, all patients should be assessed and monitored for uricemia before and during treatment. The higher frequency of benign prostatic hyperplasia or prostate enlargement and atrial fibrillation remains unclear with uncertain clinical implications.

Notably, in a post-hoc patient-level pooled analysis of four RCTs, BA did not increase the incidence of new-onset diabetes or worsening fasting glucose vs. placebo over a median follow-up of 1 year, and modestly lowered HbA1c in both patients with diabetes (−0.12%) or prediabetes (−0.06%), with consistently lowered LDL-C levels regardless of baseline glycaemic status (Leiter et al., 2022). This effect should not be disregarded, considering the opposite detrimental effect of statins on the onset of diabetes (Collins et al., 2016), with the notable exclusion of pitavastatin (Banach et al., 2022).

Considering that the evidence on the safety of BA almost exclusively derived from pre-marketing clinical trials, the post-marketing phase is crucial to establish efficacy and define the safety/tolerability profile in clinical practice, especially for drugs under additional regulatory monitoring. The CLEAR Outcome trial confirmed higher incidences of investigator-reported prespecified AEs of special interest as compared to placebo: elevations in the hepatic-enzyme level (4.5% vs. 3.0%), renal events (11.5% vs 8.6%), gout (3.1% vs 2.1%) and cholelithiasis (2.2% vs 1.2%). Myalgias were reported in 5.6% of the patients (vs 6.8%), with 8 cases of investigator-reported rhabdomyolysis (0.06%, two of which were assessed as possibly drug-related). No imbalances emerged with regard to new-onset diabetes/worsening hyperglycemia, neurocognitive disorders and adjudicated tendon rupture. As regards the observational setting, a recent retrospective cohort study on 73 patients (89% with established ASCVD, 74% with statin intolerance, 50% also receiving ezetimibe or PCSK9 inhibitors) found remarkable rates of drug discontinuation (35.9%), mostly related to treatment-emergent AEs (32.8%), primarily musculoskeletal complaints. Three cases of gout and/or hyperuricemia, and tendonitis were diagnosed, without apparent risk factors (Warden, Cardiology, Purnell, Duell, & Fazio, 2022).

3.1.4. Prescribing aspects

Based on the aforementioned benefit-risk profile, BA, administered as a 180-mg once-daily dose, received the approval of the FDA in February 2020 as monotherapy or combined with ezetimibe as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or ASCVD who require additional lowering of LDL-C (NEXLETOL - Prescribing Information, 2020; NEXLIZET - Prescribing Information, 2020). In the same year, the EMA approved its use in a similar setting, combined with a statin (in patients unable to reach LDL-C goals although at the maximally tolerated dose of a statin in addition to ezetimibe), or ezetimibe (patients already being treated with the combination of BA and ezetimibe as separate tablets with or without statin), or alone (in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone) (Nilembo - EPAR - Product Information, 2022; Nustendi - EPAR - Product Information, 2022).

The current place in therapy of BA represents an evolving issue (Ruscica, Sirtori, Carugo, Banach, & Corsini, 2022), and will also depend on the actual cost-effectiveness. Different simulation studies, based on a Monte Carlo model, estimated the potential of BA to reduce the projected need for a PCSK9 inhibitor (roughly 15-25%), especially in patients with full statin intolerance, thus possibly lowering medication expenditure by 35% (Blaum et al., 2021; Gu, Sanchez, Chauhan, Fazio, & Rosenson, 2022; Katzmann, Becker, Bilitou, & Laufs, 2022).

3.2. Lomitapide

3.2.1. Clinical pharmacology

Microsomal triglyceride transfer protein (MTP) is a lipid transfer protein essential for the assembly and secretion of hepatic and intestinal apoB-containing lipoprotein. MTP deficiency is associated with disruption of apoB-containing lipoprotein assembly in both the intestine and the liver, thus resulting in a relevant reduction of LDL-C through a mechanism independent of LDL receptor (LDLR) (Hooper, Burnett, & Watts, 2015). Lomitapide is a selective inhibitor of MTP that has been approved by EMA and FDA as an adjunctive therapy to low-fat diet and conventional lipid-lowering treatment for the treatment of adult patients with homozygous familial hypercholesterolemia (HoFH) (Juxtapid—Prescribing Information, 2019; Lojuxta—EPAR Product Information, 2022). The reduction in LDL-C levels is independent of the genotype and lomitapide can be used in all HoFH patients, including those carrying null mutations in the LDLR gene (D'Erasmo et al., 2017) and those with autosomal recessive hypercholesterolemia (D'Erasmo et al., 2022). Of note, the response of HoFH patients to the treatment with lomitapide on top of standard lipid-lowering therapy, including apheresis, shows variability, likely due to single nucleotide polymorphisms (SNPs) gene variants in *MTP* gene (Kolovou, Kolovou, Papadopoulou, & Watts, 2016); further data are needed to support this hypothesis. It is worth noting that one clinical trial (NCT04681170) is currently evaluating the safety and efficacy of lomitapide in pediatric HoFH patients (age range 5–17 years).

Since the mechanism of action of lomitapide results in an excess of available triglycerides and is commonly accompanied by an altered liver function (which may eventually evolve to fibrosis and even cirrhosis) and a lipid malabsorption syndrome with fat-soluble vitamin deficiency, patients taking lomitapide must comply with a low-fat diet to reduce gastrointestinal AEs and be monitored for liver function. Patients usually start a 5 mg/day dose that can be gradually up-titrated every 4 weeks to the maximally tolerated dose (maximum is 60 mg/day), accordingly to liver function tests and LDL-C levels achieved. In case of major AEs, dose reduction or even suspension may be required.

As anticipated, common AEs of lomitapide are gastrointestinal disturbances, which, however, become progressively less frequent in terms of severity and intensity after the drug dose escalation phase and with adherence to a low-fat diet (<20% of daily caloric intake from fat) (Stefanutti, 2020). Treatment with lomitapide may also cause fatty liver and/or increased transaminases (Stefanutti, 2020). The hepatic effects of long-term treatment with lomitapide are still unknown and need to be carefully evaluated in postmarketing studies. An analysis of the European LOWER registry, created to acquire information on long-term efficacy and safety of lomitapide in a large number of patients, showed that, with a median exposure duration of 1.98 years at a median dose of 10 mg, treatment-related AEs occurred in 54.6% of 185 patients, and serious AEs in 22.2%; gastrointestinal disorders were the most common (46.5%), 15.1% of the patients experienced transaminase elevations, of which 7 requiring further investigations for hepatic abnormalities (Underberg et al., 2020).

Lomitapide is extensively metabolised in the liver via cytochrome P-450 (CYP) 3A4 isoenzyme and dose adjustment is required when co-administered with CYP3A4 substrates such as statins

3.2.2. Cardiovascular benefit

The efficacy and safety of lomitapide were evaluated in an open-label, single-arm, phase 3 study in 23 HoFH patients treated with

gradual dose escalations of lomitapide as an adjunct to existing lipid-lowering therapy (including apheresis). Lomitapide reduced LDL-C levels by a significant 50% after 26 weeks of treatment (Blom et al., 2017). A clinical experience in Italy confirmed the efficacy and safety of treatment with lomitapide in 15 HoFH patients (D'Erasmo et al., 2017). The addition of lomitapide to conventional lipid-lowering therapy at a mean dose of 19 mg/day reduced LDL-C levels by ~70%, and allowed 46.6% of the patients to reach LDL-C levels <70 mg/dl; 80% of the patients undergoing regular LDL apheresis procedure discontinued this treatment. Other studies have confirmed the efficacy and safety of lomitapide in HoFH patients (D'Erasmo et al., 2022; Real, Arbona, Goterris, & Ascaso, 2018; Sperlongano et al., 2018; Stefanutti et al., 2016).

Lomitapide therapy was also shown to induce regression or stabilization of the carotid media-intima thickness, an established surrogate of subclinical atherosclerosis, in HoFH patients with LDL-C not adequately controlled by conventional lipid-lowering therapy (Blom et al., 2022). A modeling analysis based on data from observational and interventional studies showed that a lifelong treatment with lomitapide could increase median life expectancy by 11.7 years and time to first major atherosclerotic cardiovascular event by 6.7 years (Leipold, Raal, Ishak, Hovingh, & Phillips, 2017).

3.2.3. Final considerations

Lomitapide has been approved as a drug for the treatment of adult HoFH patients and as an add-on to standard lipid-lowering therapy, but a careful long-term safety evaluation is required. While the intensity of gastrointestinal disturbances progressively decreases with dose titration and with strict adherence to a low-fat diet, the possibility of developing fatty liver disease and its eventual progression towards more advanced stages of the disease such as steatohepatitis, fibrosis and/or cirrhosis need to be carefully evaluated in long-term treated patients.

3.3. Approaches targeting proprotein convertase subtilisin/kexin type 9 (PCSK9)

PCSK9 is a secretory serine protease synthesized primarily by the liver. It promotes the degradation of LDLR by binding LDLR, thus reducing LDL-C clearance. The formation of the PCSK9-LDLR-LDL complex causes PCSK9, LDL-C, and LDLR to enter the lysosome together to be degraded, so that LDLR on the cell surface decreases, and LDL-C degradation decreases accordingly.

Given the role of this protein, it has been suggested that pharmacological interventions that directly target PCSK9 and reduce its activity are effective in prevents PCSK9-mediated LDLR degradation, thus increasing the recycling of the LDLR to the surface of the hepatocyte, and leading to increased LDL uptake and reduced circulating LDL levels.

3.3.1. PCSK9 monoclonal antibodies

3.3.1.1. Clinical pharmacology. Among different approaches implemented to reduce PCSK9, the first one was based on mAbs directed against the protein. Of several products tested in clinical trials, alirocumab and evolocumab are currently on the market (Liu et al., 2022).

They are both fully humanized mAbs that binds specifically to human PCSK9, with quite similar pharmacokinetic and pharmacodynamic characteristics. Evolocumab is a monoclonal immunoglobulin G2 (IgG2). Following a single subcutaneous dose of evolocumab 140 mg or 420 mg, median peak serum concentrations were attained in 3–4 days, with an estimated absolute bioavailability was 72% and an effective half-life of 11–17 days. Maximum suppression of circulating unbound PCSK9 occurred by four hours (Kasichayanula et al., 2018). Alirocumab is a monoclonal immunoglobulin G1 (IgG1). The recommended starting dose is 75 mg once every 2 weeks administered subcutaneously, or 300 mg once every 4 weeks (monthly). If the LDL-C response is inadequate, the dosage may be adjusted to 150 mg administered every 2 weeks. Following a single subcutaneous dose, median peak serum concentrations were attained in 3–7 days, with an estimated absolute bioavailability was 85% and an effective half-life of 17–20 days. Maximal suppression of free PCSK9 occurred within four to eight hours (Cicero, Bove, & Borghi, 2018).

In addition to these two drugs, ongericimab (JS002), a recombinant humanized anti-PCSK9 monoclonal antibody, is currently under study for the treatment of Chinese patients with HoFH (Lin, 2022).

3.3.1.2. Cardiovascular benefit. In randomized placebo-controlled clinical studies, antiPCSK9 mAbs significantly reduced LDL-C by 55–75%, compared with placebo, either as monotherapy or in combination with a statin (Toth et al., 2017). In a meta-analysis of trials on patients who did not reach their LDL-C goal with the appropriate lipid lowering regimen, antiPCSK9 mAbs were associated with a -50% reduction in LDL-C (Squizzato et al., 2017). In statin intolerant subgroup, antiPCSK9 mAbs showed -35% reduction in LDL-C levels compared with ezetimibe (Benhuri, Ueyama, Takagi, Briasoulis, & Kuno, 2021). In patients with HeFH, antiPCSK9 mAbs significantly reduced LDL-C by approximately 50%, although a high variability of response was observed (Ge et al., 2021). This may essentially be due to the fact that these subjects primarily have pathogenic variants in the gene encoding for LDLR; some of these variants may significantly impair receptor function. Furthermore, in a small proportion of subjects, FH is determined by defects in gain-of-function of the gene coding for PCSK9. In these subjects, it is conceivable that inhibition of the PCSK9 protein may have a limited effect on reducing circulating LDL-C levels. For instance, in homozygous patients where both alleles are affected by a null mutation (resulting in residual LDLR activity that is severely impaired or absent), no or very little response to treatment targeting PCSK9 was observed (Blom et al., 2020; Raal et al., 2015). It is interesting to note that HeFH patients with a pathogenic variant leading to a mild-to-moderate impairment in LDLR activity tend to respond well to therapies directed against PCSK9, as the consequences of the dysfunctional allele are counteracted through upregulation of LDLR by overexpression of the healthy allele (Brandts et al., 2021).

Beyond the effectiveness in reducing LDL-C, antiPCSK9 mAbs were shown to have positive effect on atherosclerotic burden and also on plaque phenotype, with an increased fibrous cap thickness, decrease in maximum lipid arch, and reduction of macrophages infiltration, as demonstrated in the HUYGENS trial (Nicholls et al., 2022) and investigated in the ongoing YELLOW III trial (NCT04710368; descriptive results posted on May 3rd, 2023).

In the FOURIER trial, evaluating the effect of evolocumab on cardiovascular outcomes in patients with ASCVD, active treatment significantly reduced the risk of the primary end point (a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, hazard ratio, 0.85; 95% CI, 0.79–0.92) and the key secondary end point (the composite of cardiovascular death, myocardial infarction, or stroke; hazard ratio 0.80; 95% CI, 0.73–0.88) over a median follow-up of 2.2 years (Sabatine et al., 2017). In the open-label extension (FOURIER-OLE), with an overall maximum exposure of 8.4 years, patients originally randomized to evolocumab versus placebo had a 15% lower risk of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina or coronary revascularization (hazard ratio 0.85; 95% CI, 0.75–0.96) (O'Donoghue et al., 2022). Moreover, 24% patients achieved LDL-C levels of <20 mg/dL, and it was associated with lower risk of cardiovascular outcomes, without significant safety concerns (Gaba et al., 2023).

In the ODYSSEY OUTCOME trial, after a median follow-up of 2.8 years, alirocumab treatment was associated with a significant 15% reduction in the primary end point (a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization, hazard ratio 0.85;

95% CI, 0.73–0.98) compared to placebo in patients who had an acute coronary syndrome 1 to 12 months earlier. The absolute benefit was greater among patients who had a baseline LDL-C level of 100 mg/dL or more (Schwartz et al., 2018). A meta-analysis on pooled results from 28 RCTs comprising 62,281 participants showed that the LDL-C reduction with antiPCSK9 mAb was shown to be associated with a significant reduction of CV events compared with placebo (odds ratio 0.83 [95% CI, 0.78–0.87]), without significant impact on cardiovascular mortality. Both myocardial infarction (odds ratio 0.78 [95% CI, 0.72–0.84]) and stroke (odds ratio 0.77 [95% CI, 0.67–0.89]) were significantly reduced following the treatment with an antiPCSK9 mAb (Casula et al., 2019).

Safety Aspects

Both evolocumab and alirocumab appear to be well tolerated (Casula et al., 2019; Navarese et al., 2015). In clinical trials, the overall rate of AEs with PCSK9 inhibitors was similar to placebo. Serious AEs appear uncommon. The most commonly reported AEs are local injection site reactions (e.g., erythema, pain, or bruising), occurring in 6-10% of treated patients (Jones et al., 2016). PCSK9 mAbs do not appear to cause muscle toxicity or elevated liver enzymes (Zhang et al., 2015). Drug-neutralizing antibodies were detected in 1.2% of alirocumab treated patients, but without consistent loss of LDL-C-lowering efficacy (Roth et al., 2017). Drug neutralizing antibodies to evolocumab were not detected during clinical trials.

Low LDL-C levels in RCTs of antiPCSK9 mAbs have raised a concern about the risk of cognitive impairment (Robinson et al., 2015; Sabatine et al., 2015). In two meta-analyses of RCTs and in the EBBINGHAUS study, a sub-study of the FOURIER trial evaluating the cognitive deficits, neurocognitive adverse events in the active groups were not significantly different from those reported in the control groups (Bai, Gong, Li, & Wang, 2018; Karatasakis et al., 2017). These findings were supported by a Mendelian randomization study which found no causal relationship between inhibition of PCSK9 function and neurodegenerative diseases (Benn, Nordestgaard, Frikke-Schmidt, & Tybjærg-Hansen, 2017). Concerning long-term AEs, as already observed for statins (Casula et al., 2017), a possible risk of new-onset type 2 diabetes (T2DM) with antiPCSK9 mAbs treatment has been also hypothesized. Mendelian randomisation studies showed that patients carrying loss-of-function PCSK9 genetic variants showed an increased risk of developing T2DM, besides lower LDL-C levels. RCTs with anti-PCSK9 MAbs however showed no effect on the risk (Carugo, Sirtori, Corsini, Tokgozoglu, & Ruscica, 2022). A possible explanation of the discrepancy is related to the activity on mAbs, targeting mainly circulating PCSK9, with a limited impact on LDL-R expression in pancreatic cells and on the risk of T2DM.

Data form pharmacovigilance studies (i.e., spontaneous reporting systems) found signals of neurocognitive and hyperglycaemic disorders (mild hyperglycaemia more frequently reported in subjects with diabetes), thus strengthening the importance for maintaining vigilance, especially in patients with risk factors, and the need for long-term clinical trials and observational studies to further explore these potential risks (Goldman et al., 2022; Gouverneur et al., 2021).

3.3.1.3. Prescribing aspects. Based on considerable evidence of effectiveness and a good safety profile, in 2015 alirocumab and evolocumab received approval by the FDA and the EMA. They are both indicated as an adjunct to diet, alone or in combination with other LDL-C-lowering therapies, in adults with primary hyperlipidemia, including HeFH, and in adults with established ASCVD (Praluent Prescribing Informatrion, 2021; Praluent—EPAR Product Information, 2023). Evolocumab was also approved by EMA for use in adults and adolescents aged ≥ 10 years with HoFH in combination with other lipid-lowering therapies, and received FDA approval in aged 10 years or older with HoFH and HeFH (Repatha—EPAR Product Information, 2022; Repatha—Prescribing Information, 2022).

According to last versions of American and European guidelines on the management of dyslipidaemias (Arnett et al., 2019; Grundy et al., 2019; Mach et al., 2020), the use of a PCSK9 inhibitor is recommended for secondary prevention in FH patients, at very-high risk and not achieving their goal on a maximum tolerated dose of a statin and ezetimibe. European guidelines also specifically stated that if a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor may be considered as further option, after adding ezetimibe (Mach et al., 2020).

Evidence from the observational setting showed an efficacy comparable to that observed in trials, and an appreciable level of adherence to therapy. In an analysis of Canadian patients treated with evolocumab, most with a diagnosis of atherosclerotic cardiovascular disease and/or FH, with mean (± SD) LDL-C concentration at baseline of 143 (± 66) mg/dL, a 58.7% decrease from baseline was reached and an LDL-C concentration < 70 mg/dL was achieved by 77.5% of patients (Gupta et al., 2022). A recent study in a Prague-based hospital showed a -59.4% reduction in LDL-C after 12 weeks of antiPCSK9 mAb treatment; the effect was persistent to become even stronger, with a –62.6% at 2 years (Altschmiedová, Todorovová, Šnejdrlová, Šatný, & Češka, 2022). An Italian study on patients taking evolocumab or alirocumab in association with statin and/or ezetimibe showed that LDL-C declined significantly during 4 years, from −60.8% at first year to −73.7% at fourth year (Derosa et al., 2022). Another study reported that among patients with a clinical diagnosis of FH, 85.4% patients receiving a PCSK9 inhibitor achieved a ≥50% reduction in LDL-C, compared with 50.2% of patients not receiving a PCSK9 inhibitor (Razek et al., 2018). The majority of studies reported high levels of adherence and no serious treatment-emergent AEs (Gupta et al., 2022; Nanchen et al., 2022). Notably, a recent Italian nation-wide registry on 798 patients (median LDL-C reduction of 64.9%) found a very high adherence (3.5% of patients discontinued) and persistence (97.5% at 18 months) (Gargiulo et al., 2023).

Despite their safety and cardiovascular benefits, their use in clinical practice was initially scarce, mainly as a consequence of their high cost (over 14,000 USD [US dollars] per year on average in 2017) (Karalis et al., 2018). In 2018, the cost of both alirocumab and evolocumab were reduced, though with only slightly increased use of these drugs (Attipoe-Dorcoo et al., 2021; Dayoub et al., 2021). Recent reports confirmed the cost-effectiveness of antiPCSK9 mAbs and supported their reimbursement (Grégoire et al., 2022), mainly if eligible patients are at very high CV risk and far from the LDL-C goal despite the optimization of background lipid-lowering therapy (Fogacci et al., 2022; Marquina et al., 2020). Nevertheless, several barriers to widespread use of antiPCSK9 mAbs remain, as for example still high drug prices patient cost sharing, and reimbursement threshold, with strong variability between geographical contexts, different income levels, and types of healthcare, together with implementation gaps, such as poor use of combination therapy.

3.3.2. Inclisiran

3.3.2.1. Clinical pharmacology. RNA interference is a physiological defense mechanism for the invasion of viruses and other unwanted RNAs in eukaryotic cells. RNA interfering molecules, both endogenous micro RNAs (miRNAs) or exogenously introduced small interfering RNAs (siRNAs), silence the expression of specific genes by targeting messenger RNA (mRNA) for degradation in a sequence-specific manner (Levin, 2017). In recent years, RNA interference technology, using synthetic structurally well-defined short double-stranded siRNA, has advanced rapidly (Ranasinghe, Addison, Dear, & Webb, 2022). In this context, inclisiran is a first-in-class gene silencing drug, which specifically targets hepatic PCSK9 mRNA and inhibits its translation (Khvorova, 2017). In particular, inclisiran is a siRNA duplex oligonucleotide (one 2'-deoxy, 11 2'-fluoro, and 32 2'-O-methyl modified

nucleotides for a total of 44 base pairs) conjugated to triantennary N-acetylgalactosamine that specifically targets inclisiran to hepatocytes. Inside the hepatocytes, it acts by binding to the RNA induced silencing complex (RISC) and blocking the translation of PCSK9 mRNA, thereby reducing PCSK9 synthesis and its secretion into the extracellular milieu (Soffer, Stoekenbroek, & Plakogiannis, 2022).

The targeting of inclisiran to the liver is positive for a number of reasons. First, the liver is the organ where the most part of PCSK9 is produced. Then, it reduces the theoretical (but not yet demonstrated) risk of off-target inhibition, as PCSK9 is also expressed in other tissues than liver (i.e., lungs, pancreas, brain) (Stoekenbroek, Lambert, Cariou, & Hovingh, 2018). Interestingly, a comprehensive search against the human transcriptome revealed only 20 potential off-target transcripts, some of which are not normally expressed in the liver (Ranasinghe et al., 2022). Furthermore, the N-acetylgalactosamine-mediated liver specificity allows for the use of low cumulative doses, considering that at the relevant clinical plasma concentrations, inclisiran is 87% protein bound (Lamb, 2021). Thus, the systemic exposure to inclisiran is limited and it is no longer detectable in the circulation 48h after administration; notwithstanding non-negligible renal clearance, available data confirmed no significant impact of mild, moderate and severe renal impairment on the efficacy and safety of inclisiran, with no need for dose adjustment (Wright et al., 2020). The phase I ORION-6 trial enrolled 28 participants (16 with hepatic impairment) and found no significant pharmacodynamic changes (PCSK9 and LDL-C levels) with 2-fold increased exposure in subjects with moderate liver impairment, without the need for dose adjustment (Kallend, Stoekenbroek, He, Smith, & Wijngaard, 2022). No pharmacokinetic interactions are known or expected (Strilchuk, Fogacci, & Cicero, 2019).

3.3.2.2. Cardiovascular benefit. The efficacy of inclisiran has been evaluated in three pivotal, randomized, double-blind phase 3 studies (ORION-9, ORION-10, and ORION-11), which confirmed its ability to achieve early, marked, sustained and reversible LDL-C reductions compared with placebo in patients with elevated LDL-C despite maximally tolerated statin therapy (with or without additional lipid-lowering therapy) (Raal, Kallend, et al., 2020; Ray et al., 2020). A meta-analysis of five RCTs including 4226 patients concluded that treatment with inclisiran yielded an impressive reduction in serum levels of PCSK9 (MD= −78.23%, 95% CI: −86.74–69.71) and LDL-C (MD= −45.48%, 95% CI: −50.36–40.61%) throughout the considered studies. Furthermore, treatment with inclisiran significantly improved the plasma levels of total cholesterol (MD= −13.67%, 95% CI: −20.78%,−6.57%), non-HDL cholesterol (MD= −39.45%, 95% CI: −43.6%,−35.31%), apolipoprotein B (MD= −34.58%, 95% CI: −38.78%, −30.78%), HDL-C (MD= 8.29%, 95% CI: 4.66%,11.93%), and Lp(a) (MD= −20.9%, 95% CI: −25.8%, −15.99%) (Cicero, Fogacci, Zambon, Toth, & Borghi, 2022). In ORION-3 (a 4-year open-label extension study of ORION-1) trial confirmed the lack of any compensatory or escape mechanisms and found a sustained effect of inclisiran (averaged mean reduction of LDL-C cholesterol was 44.2%, with reductions in PCSK9 ranging from 62.2% to 77.8%). Of note, in the switching arm where patients received first open label twice-monthly evolocumab, the LDL-C levels lowered by approximately 61% over 1 year through 25 injections, with an averaged mean reduction of LDL-C of 45.3% over 3 years achieved through 7 injections. Although these data suggested that past exposure or treatment with a mAb against PCSK9 did not alter the efficacy of inclisiran, it should be acknowledged that mean LDL-C reduction and number of patients reaching LDL-C goal was significantly higher during the evolocumab treatment phase than after switch to inclisiran injection (Ray et al., 2023).

An updated pooled analysis of ORION-9, −10 and −11, (N. 3655 patients followed-up over 18 months) concluded that inclisiran is associated to a significant reduction of composite MACE (OR 0.74; 95% CI 0.58–0.94), but not of fatal and non-fatal myocardial infarction or fatal and non-fatal stroke (Ray, Raal, et al., 2023). The longer-term impact of Inclisiran therapy on CV outcomes is being prospectively evaluated in the HPS-4/TIMI 65/ORION-4 trial (NCT03705234). Because of enrollment challenges related to the global COVID-19 pandemic, primary completion (initially expected for December 2024) is now estimated to be in July 2026. Additionally, the phase 3 VICTORION-2P trial (NCT05030428) evaluating inclisiran sodium for patients with established ASCVD is also currently ongoing (estimated completion in October 2027).

3.3.2.3. Safety aspects. The most frequent inclisiran AEs were transient injection-site reactions (any reaction: OR= 5.86, 95% CI: 3.44,9.98; mild reactions: OR= 5.19, 95% CI: 1.68,16.07; moderate reactions: OR= 13.37, 95% CI: 3.17,56.46). In ORION-9, ORION-10 and ORION-12, a total of 99 injection-site reactions on 1833 patients exposed (5.4%), while 15 on 1822 in placebo-treated patients (0.8%) (Cicero et al., 2022). This incidence seems to be higher than the one observed with PCSK9 (15 injection-site reactions leading to discontinuation per 1,000 subjects over a 5-year interval) (Li et al., 2022). A higher incidence of bronchitis (OR= 1.58, 95% CI: 1.10,2.26) in inclisiran treated patients was also observed, whose cause is yet to be clarified (Cicero et al., 2022). In fact, a recent paper has clearly highlighted that inclisiran did not exert any significant effect on immune cells and inflammatory biomarkers such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) (Landmesser et al., 2021). No additional safety concerns emerged from over approximately 5 years of exposure to inclisiran from the start of ORION-1 through to the end of ORION-3, also in patients switching from evolocumab. In particular, none of the 8 deaths were considered to be related to the study medication, and only 4 patients experienced treatment-emergent serious AEs possibly related to study drug (as reported by the investigator). Treatment-emergent hepatic events occurred in 10% of patients in the inclisiran-only arm and 9% of patients in the switching arm; two were serious, but none meet criteria for Hy's Law (Ray, Troquay, et al., 2023).

3.3.2.4. Prescribing aspects. Inclisiran is prepared as a prefilled syringe (containing 300 mg inclisiran sodium, equivalent to 284 mg inclisiran in 1.5 mL water for injection) for subcutaneous administration. Inclisiran should be stored at controlled room temperature (20–25°C [68–77°F]), with allowable excursions between 15°C and 30°C [59°F and 86°F]), and has a shelf life of 2 years. After the first subcutaneous injection, it is administered again at 3 months, and then every 6 months thereafter (twice a year versus 12-26 injections of PCSK9 inhibitors per year) (Banerjee et al., 2022).

Based on the available clinical evidence, inclisiran has recently been approved by the EMA (December 9th, 2020) and the FDA (December 22nd, 2021), for the management of residual hypercholesterolemia in patients already affected by cardiovascular disease or by HeFH not reaching the desired LDL-goal with maximally tolerated statin treatment (Leqvio Prescribing Information, 2021; Leqvio—EPAR Product Information, 2022).

3.3.3. New alternative approaches to inhibiting PCSK9-mediated LDLR degradation

LDL-C reduction can be achieved by acting on PCSK9 at different levels: (i) blocking of PCSK9/LDLR binding (as obtained with mAbs, but also with vaccines, adnectines, or either PCSK9/LDLR binding site mimetic peptides), or (ii) inhibiting PCSK9 synthesis and expression in vivo (as obtained with inclisiran, but also using CRISPR/Cas9-based genome-editing technology, antisense oligonucleotides [ASO], or small molecules) (Ahamad & Bhat, 2022).

The development of peptide-based anti-PCSK9 vaccines is an alternative method for the long-term suppression of PCSK9. Compared to mAbs, the PCSK9 vaccine offers simple and affordable production, less frequent dosing, and long-lasting effects. AT04A, a short peptide-based anti-PCSK9 vaccine, demonstrated to trigger a strong and sustained immune response against PCSK9. The first dose was found to be safe

in phase I clinical trial on healthy adults, and a booster dose after a year decreased LDL-C levels by 13.3% (Zeitlinger et al., 2021). VXX-401 is another synthetic peptide vaccine, able to achieve durable lowering of LDL-C cholesterol in non-human primates, and selected to be evaluated into a phase I first-in-human clinical trial (*NEWS RELEASE: Vaxxinity's Anti-PCSK9 Candidate Demonstrates Durable LDL Cholesterol Lowering in Non-Human Primates*, 2022).

Adnectin is a new PCSK9-targeted approach developed to extend the dosing interval. Adnectins are recombinant fusion proteins that offer many benefits over mAbs, such as small size, lower expense, easier production, and a high affinity with a quick onset of action. In a phase I clinical study, BMS-962476 decreased LDL-C levels by 48% (Stein, 2014). Another potent adnectin, lerodalcibep (LIB003) at a dose of 300 mg was found to reduce LDL-C levels by 64.1%, and it is currently being evaluated in phase III trials (Turner, 2020).

Analog peptides play an inhibitory role by blocking the binding between PCSK9 and LDLR. Several peptides are being developed as once-a-day oral anti-PCSK9 therapeutics (Tombling, Zhang, Huang, Craik, & Wang, 2021; Tucker et al., 2021). At present, two peptide PCSK9 inhibitors, MK-0616 and NNC03850434 (NN6434), have progressed to phase II clinical trials. MK-0616 is a next generation macrocycle that, in a recent phase 2b study, reduced LDL-C levels by 40-60% at oral doses of 6-30 mg in subjects with wide range of ASCVD risk (Ballantyne et al., 2023).

Genome engineering using the CRISPR-Cas9 system have been found to effectively reduce PCSK9 expression Recently, a single-dose treatment of CRISPR base editors, delivered in the liver of cynomolgus monkeys, lowered LDL-C levels by 60% for 8 months (Lee et al., 2023). VERVE-101 is an investigational *in vivo* CRISPR-based editing medicine, designed to be a single-course treatment to permanently turn off the PCSK9 gene in the liver to reduce LDL-C. In non-human primates it was well tolerated and led to 69% lower LDL-C, with durable effects. VERVE-101 is currently being evaluated in a phase I clinical trial; initial clinical results from the dose escalation portion of the heart-1 clinical trial including safety parameters, blood PCSK9 level, and blood LDL-C level are expected in the second half of 2023. PBGENE-PCSK9 applies ARCUS genome editing to knockout the PCSK9 gene using adeno-associated virus delivery (Arnould et al., 2011). After promising results in pre-clinical studies, PBGENE-PCSK9 will be soon advanced through human phase I studies.

ASOs consist of short, single-stranded nucleotides able to interfere with gene expression by binding to the target mRNA directly, within the nucleus or cytoplasm. Several ASOs have been developed in the past decade. A phase II clinical trial for the third-generation PCSK9 antisense molecule CIVI007 (cepadacursen sodium) was recently completed, showing a reduction of about 60% of LDL-C after a monthly administration of 75 mg subcutaneously (NCT04164888). The same molecule is now under development for oral administration (CIVI008) (Arnold & Koenig, 2022).

Finally, CVI-LM001 (1) is a fluorobenzenesulfonate derivative of corydaline that acts by suppressing the expression of the PCSK9 gene (Liu, 2020). An oral-administered 300 mg dose of CVI-LM001 (1) for 28 days reduced LDL-C levels by 26.3% in participants with elevated LDL-C levels in the phase Ib study. A phase II clinical trial to assess the effectiveness and safety in people with hypercholesterolemia is currently recruiting (NCT04438096).

3.4. Angiopoietin like-3 inhibitors

Angiopoietin like-3 (ANGPTL3) is a protein produced essentially in the liver that play a key role in the metabolism of lipoproteins. Angptl3 acts primarily by inhibiting the activity of lipoprotein lipase (LPL) in the vasculature, resulting in a reduced clearance of triglyceride (TG)-rich lipoproteins and increased circulating levels of TG; it also inhibits the activity of endothelial lipase (EL), an enzyme involved in the metabolism of high density lipoproteins (HDL) (Tikka & Jauhiainen, 2016). It is worth noting that ANGPTL3-mediated regulation of EL is not limited to its effect on HDL-C but is also required for the modulation of LDL-C levels when LDLR is absent (Adam, et al., 2020).

Whole-exome sequencing in two siblings clinically diagnosed with combined hypolipidemia led to the identification of two nonsense mutations in *ANGPTL3* gene. Both subjects were compound heterozygotes for these mutations and exhibited extremely low plasma levels of LDL-C, HDL-C, and TG (Musunuru et al., 2010). Since then, other mutations in ANGPTL3 have been identified, all associated with a hypolipidemic phenotype (Martín-Campos et al., 2012; Minicocci et al., 2012; Musunuru et al., 2010; Noto et al., 2012; Pisciotta et al., 2012) and a reduced risk of coronary disease (Dewey et al., 2017; Stitziel et al., 2017). These observations have suggested ANGPTL3 as a pharmacological target for the treatment of hypercholesterolemia; with reduction in LDL-C levels being determined through an LDLR-independent mechanism, ANGPTL3 inhibition has been proposed as an interesting tool for the management of hypercholesterolemia in HoFH.

Several strategies have been proposed to inhibit ANGPTL3, including a monoclonal antibody (evinacumab) targeting plasma ANGPTL3, as well as an antisense oligonucleotide (vupanorsen) and a small interfering RNA (ARO-ANG3), both targeting the hepatic synthesis of ANGPTL3. Another possible approach is VERVE-201, an investigational *in vivo* CRISPR base editing therapy designed to alter a single DNA base in the ANGPTL3 gene, permanently inactivate hepatic expression, and thereby durably lower LDL-C and triglyceride concentrations.

3.4.1. Evinacumab

Evinacumab is a fully human monoclonal antibody that was shown to reduce circulating lipid levels and atherosclerotic lesion size in experimental models (Dewey et al., 2017; Gusarova et al., 2015). When tested in healthy volunteers with mildly-to-moderate elevated levels of TG or LDL-C, evinacumab reduced dose-dependently both lipid levels (Dewey et al., 2017). Evinacumab was then tested in HoFH patients. An open-label phase 2 study showed that evinacumab was able to reduce LDL-C levels by 49%; other lipids were also significantly reduced despite variability in the response, evinacumab reduced LDL-C levels in all patients, including those carrying null mutations (Gaudet et al., 2017). The reduction in LDL-C levels was proven to depend on an increased clearance of apoB-containing lipoproteins, independently of LDLR (Reeskamp et al., 2021).

The phase 3 HELIPSE HoFH study enrolled 65 patients who received placebo or evinacumab every 4 weeks on top of their lipid-lowering therapy. After 24 weeks, evinacumab reduced LDL-C by 49% compared with placebo, with an absolute difference in LDL-C of 132 mg/dL (Raal, Rosenson, et al., 2020). When analyzed by genotype, patients with null-null mutations had LDL-C reductions similar to those observed in patients with non-null mutations. An interesting observation is that evinacumab induced a profound plaque reduction in two severely affected young HoFH patients after a 6-month treatment period (Reeskamp et al., 2021). A recent case report of a long-term lipid-lowering therapy involving drugs with LDLR-independent mechanism, including lomitapide and evinacumab, showed remarkable improvement in LDL-C levels (>90% following the addition of lomitapide and evinacumab), disappearance of xanthomatosis, and regression in atherosclerotic plaques (Khoury, Lauzière, Raal, Mancini, & Gaudet, 2023). The efficacy of evinacumab has been confirmed also in clinical experience, with 7 HoFH patients already receiving best standard of care, who showed a ~47% reduction in LDL-C levels, with no major adverse event reported (Stefanutti, Chan, Di Giacomo, Morozzi, & Watts, 2022). Based on the results of the ELIPSE HoFH trial, both FDA (February 11th, 2021) and EMA (June 17th, 2021) have approved the use of evinacumab in adults and adolescents aged 12 years and older with HoFH (Evkeeza Prescribing Information, 2021; Evkeeza—EPAR Product Information, 2022). On March 21st, 2023, the FDA extended its use in aged 5 to 11 years.

Although the knowledge of exact mechanism(s) governing the ANGPTL3-mediated regulation of LDL-C is still incomplete, inhibiting ANGPTL3 lowers LDL-C by limiting the production of LDL particles (Adam, et al., 2020). Indeed, following ANGPTL3 inhibition, the activity of EL is derepressed, leading to extensive remodelling of VLDL and the formation of lipid-depleted remnant particles that are efficiently cleared from the circulation (Adam, et al., 2020). This EL-dependent alternative pathway, likely irrelevant when LDLR is functioning properly, becomes of increasingly importance when LDLR is dysfunctional (Adam, et al., 2020).

Evinacumab has been tested also in patients with or without HeFH who had refractory hypercholesterolemia, in whom a 50% reduction in LDL-C levels was reported (Rosenson et al., 2020), and in patients with high and severe hypertriglyceridemia, who showed substantial reduction in TG and VLDL-C levels (Ahmad et al., 2019, 2021).

4. Evidence-based management of LDL-C: an evolving issue

We are witnessing a rapidly evolving landscape of contemporary management of hypercholesterolemia, with potential paradigm shift in the relevant treatment, not only in terms of therapeutic goal, but also in terms of pharmacological strategies (Ferraro et al., 2022). The advent of PCSK9 inhibitors, while providing additional opportunity within the pharmacological armamentarium, poses new challenges to clinicians in the proper selection (and combination) of the right drug (s) for the right patient.

While the current mantra of *the lower the better* for LDL-C is still valid and recognized by evidence and current AAC/AHA and ESC/EAS guidelines (Ference et al., 2017; Knuuti et al., 2020; Mach et al., 2020; Silverman et al., 2016), recent observational data from DaVinci study and GOULD registry showed the suboptimal use of lipid-lowering therapy, especially in subjects at higher risk (Cannon et al., 2021; Ray et al., 2021). Therefore, there is increasing interest and debate in optimizing pharmacological therapies, especially for non-statin drugs, to reduce ASCVD risk as early as possible through an upfront approach (Banach et al., 2021; Banach et al., 2021; Banach et al., 2022; Banach & Penson, 2021; Ray et al., 2022). This so-called *strike early and strike strong* approach could be theoretically useful in the immediate aftermath of an acute coronary syndrome, considering that all lipid-lowering agents are expected to reach almost the maximum extent of LDL-C reduction after 2 weeks of therapy (Krychtiuk et al., 2022). Of note, the transition towards an early and more aggressive strategy is still debated, although it represents a current approach in the cardiovascular area especially in the treatment of heart failure and hypertension, where a first-line combination strategy is supported by relevant guidelines.

Conversely, some authors still supported the importance of a gradual stepwise approach (Averna et al., 2021; Kakavand et al., 2022), which should take into account the efficacy (on LDL-C and hard cardiovascular endpoints) of each pharmacological class, potential contraindications, warnings and precautions, relevant adverse effects, and monitoring parameters. This view of progressive treatment intensification is also endorsed by the 2021 ESC cardiovascular prevention guidelines (Visseren et al., 2021). This traditional approach might be ideal especially in complex scenarios such as elderly frail poly-treated patients with comorbidities (e.g., diabetes), who are susceptible to clinically relevant drug interactions and are likely to have pharmacokinetic/pharmacodynamic changes affecting drug response, thus increasing the likelihood of side effects and adverse drug reactions.

Here below, some pharmacological pearls are provided to address, on an individual basis, the multifaceted issue of drug tailoring and optimization of treatment.

First, statins remain the drugs of choice for initial LDL-C reduction given the large body of efficacy and safety data. Statin monotherapy reduces LDL-C levels by approximately 30 (low intensity) to 50% (high intensity). Irrespective of the statin used, each doubling of the dose produces an extra reduction of about 6 percentage points in LDL-C (e.g., 43% vs 49% reductions with atorvastatin 20 mg vs 40 mg daily). In patients with documented statin intolerance, the maximal tolerated statin at even ultra-low doses (e.g., rosuvastatin 2.5 mg three times per week) should be considered instead of abandoning statins altogether.

Second, there is general consensus on the theoretical incremental benefit of combination regimens with regard to the ability to lower LDL-C (Masana, Ibarretxe, & Plana, 2016), although a wide variability among individuals is expected, and some authors have proposed to consider markers of cholesterol absorption and fecal excretion to individualize the initial choice (Lütjohann, Stellaard, Mulder, Sijbrands, & Weingärtner, 2019). Therefore, monitoring LDL-C levels 4-6 weeks after any treatment strategy initiation or change is recommended. Interestingly, the maximum LDL lowering to be achieved by combined oral therapy (high-intensity statin and ezetimibe) is 65%, similar to PCSK9 inhibitors (60%), with the maximum LDL-lowering efficacy (84%) obtained by triple therapy (high-intensity statin plus ezetimibe plus PCSK9 inhibitors). Interestingly, the substitution of moderate-intensity statin in this triple therapy produced an 82% reduction (only 2% less that using high-intensity statins). On the other hand, a high-intensity statin plus PCSK9 inhibitors, without ezetimibe, reduces LDL by 80%, so the contribution of ezetimibe to high-intensity triple therapy is 4%. All these aspects should be taken into consideration especially when prescribing PCSK9 inhibitors (Masana, Ibarretxe, & Plana, 2020). There are no head-to-head comparisons of inclisiran with PCSK9 mAbs, although the LDL-C lowering response to inclisiran appears approximately 10% less than seen with PCSK9 mAbs. There is no current evidence or mechanistic plausibility that combining inclisiran with PCSK9 mAbs provides additional efficacy in LDL-C lowering or cardiovascular outcomes benefit; therefore, inclisiran should be used in place of PCSK9 mAbs. Theoretically, a quadruple combination of high-intensity statins + ezetimibe + bempedoic acid + PCSK9 inhibitor could result in >85% of LDL-C reduction (Banach et al., 2023).

Third, recent evidence suggested that the "high-intensity statin therapy" concept could be substituted by the "high-intensity lipid lowering therapy" approach (Masana et al., 2020). In fact, IMPROVE-IT and RACING studies paved the way to consider the early combination therapy in patients at very-high ASCVD risk (Cannon et al., 2015; Kim et al., 2022). Of note, the RACING trial (median follow-up 3 years) demonstrated that the combination of a moderate-intensity statin and ezetimibe was non inferior to high-intensity statin monotherapy, and showed a lower rate of discontinuation or dose reduction of study drug due to intolerance in the combination regimen (4.8% vs 8.2%) (Kim et al., 2022). These findings might reflect the clinical practice (including the potential nocebo effect in the high-intensity statin group) and further support the role of early combination approach to improve adherence. Accordingly, a recent dose-response simulation model predicted that combining BA with the lowest statin dose (e.g., atorvastatin 20 mg) would achieve a similar degree of LDL-C lowering as quadrupling that statin dose (e.g., atorvastatin 80 mg) (Jadhav et al., 2022), thus reducing the likelihood of side effects. Very recently, the open-label LODESTAR trial demonstrated the noninferiority of the treat-to-target strategy (with an LDL-C level between 50 and 70 mg/dL as the target) as compared with a high-intensity statin strategy on 3-year composite of death, myocardial infarction, stroke, or coronary revascularization in 4400 relatively-low risk patients with coronary artery disease, with a numerically lower rate of secondary endpoints (new-onset diabetes, end-stage kidney disease, or composite of laboratory abnormalities), thus suggesting that a tailored approach may account for individual variability in therapeutic response to statin therapy (Hong et al., 2023).

Fourth, there are further important considerations in the addition and choice of non-statin therapies, especially in specific patient populations (e.g., pregnant women, elderly patients, patients with diabetes) (Fig. 3). These considerations include the extent of available evidence for ASCVD risk reduction, safety and tolerability, potential for drug-drug interactions, cost, convenience and medication storage, pill burden, frequency and route of administration, and, importantly, patient preferences. The importance of patient engagement and informed

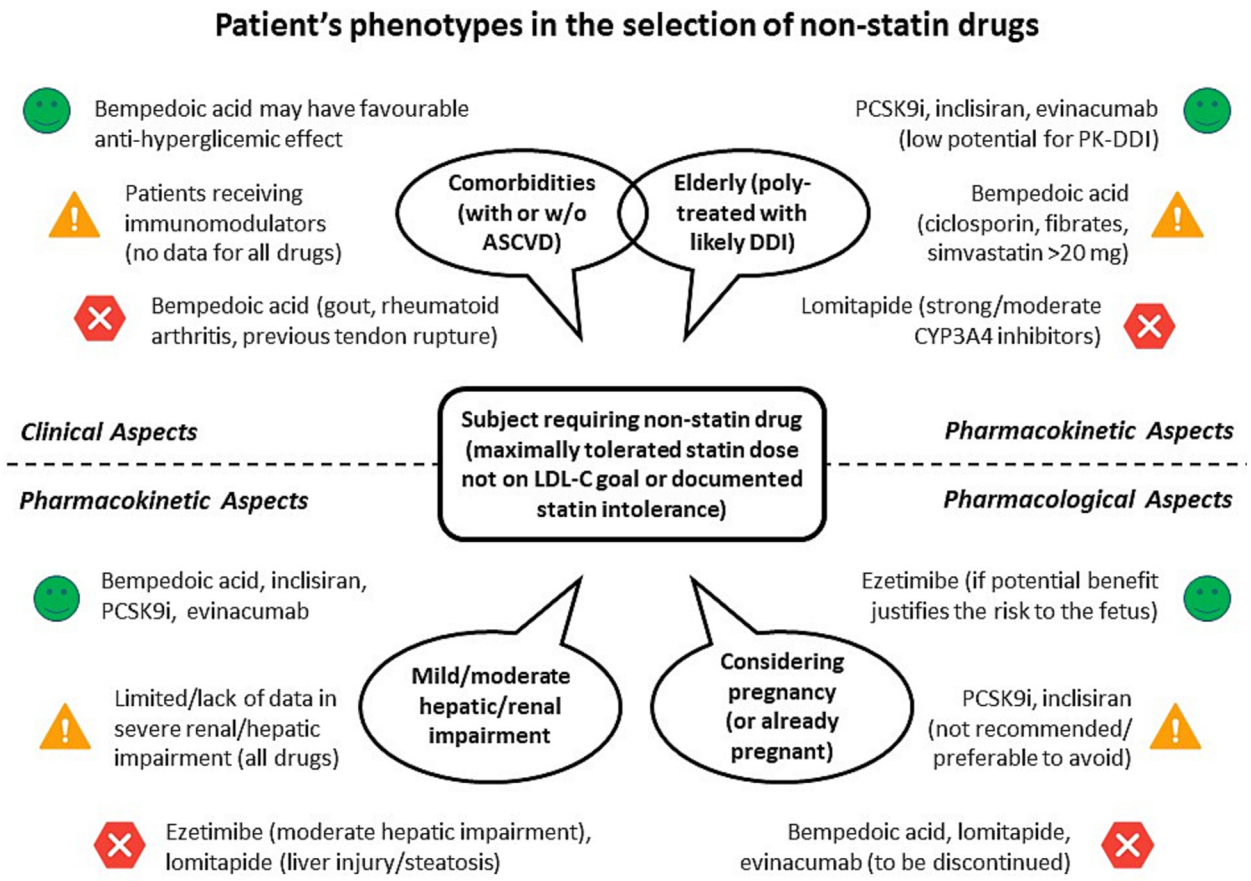

Fig. 3. Additional clinical and pharmacological aspects in the selection and monitoring of non-statin drugs.
Please refer to the relevant summary of product characteristics or prescribing information for details.
Green symbol: the drug can be safely used; orange symbol: Uncertainty in the use, possibly due to the lack of data. Monitoring and/or dose adjustment is recommended; red symbol: contraindicated or not recommended.
ASCVD: atherosclerotic cardiovascular disease; CYP: cytochrome P450; PCSK9i: Proprotein convertase subtilisin/kexin type 9 inhibitors (monoclonal antibodies alirocumab or evolocumab); PK-DDI: pharmacokinetic drug-drug interactions.

choice is supported by the 2022 ACC clinical decision pathway (Committee et al., 2022).

Based on the overall evidence, ezetimibe and PCSK9i should be prioritized in those at the highest ASCVD risk not reaching the LDL-C target or maximally tolerated statin dose or with documented statin intolerance. Ezetimibe may be preferred as initial choice in patients who require <25% additional lowering of LDL-C, with recent acute coronary event (<3 months), and considering ease of use, patient preference and cost (depending on local reimbursement criteria). Moreover, in patients with pill burden, fixed combinations may be favoured. A recent international multidisciplinary panel that included patients drafted 10 recommendations: a strong recommendation in terms of quality of the evidence was only provided for patients at high or very high risk, intolerant to statins, for using ezetimibe or PCSK9i, with suggestion of using ezetimibe first (weak) (Hao et al., 2022). The twice-yearly dosing regimen of inclisiran may be attractive in patients with demonstrated poor adherence to antiPCSK9 mAbs, serious or intolerable side effects or unable/uncomfortable to self-inject. The current place in therapy of BA represents an evolving issue (Ruscica et al., 2022), although its favourable pharmacokinetics and safety profile, coupled with the opportunity of a fixed-dose combination with ezetimibe, should not be overlooked in the perspective of patient's adherence. Recent position statements concluded that BA may represent a cost-effective therapeutic choice (third line therapy), especially in combination with ezetimibe, in patients with high or very high cardiovascular risk who are not far from individual LDL-C target or when the prescription of PCSK9i is not allowed due to local reimbursement criteria (Averna, Bilato, Sesti, Network, & on Bempedoic Acid., 2022; Patti et al., 2022). The results of the CLEAR Outcomes trial have clarified the role of BA in patients intolerant to statins at high risk of ASCVD (Nissen et al., 2023), thus making BA a potential choice for upstream approach in subjects with high/very high cardiovascular risk before PCSK9 therapies (Banach et al., 2023). The role of evinacumab and lomitapide is attractive in HoFH patients poorly responsive to statins or PCSK9 inhibitors, although appropriate management by specialized centers is required.

In Fig. 4, we propose a simplified flow-chart integrating the AHA and the EAS/ESC guidelines to LDL-C management in clinical practice, also including some recent opinion papers suggesting an early statin-ezetimibe combination use as first-line treatment in most of the subjects (Averna et al., 2021; Elis, 2023). A single pill may support adherence while achieving a more rapid reduction of the LDL-C levels (to be re-assessed after 4-6 weeks) with reduced adverse effects. The proposed approach considers the patient baseline LDL-C values and the estimated cardiovascular risk (which may vary depending on the adopted score/algorithm), the patient ability to tolerate statins, the LDL-C goal and values reached, as well as the expected efficacy in terms of LDL-C reduction. Of note, the actual feasibility of the approaches will depend on the drug cost covered by national health systems and insurances.

5. Closing remarks

The pharmacological opportunities for targeting LDL-C have considerably expanded in recent years. Different medications have been

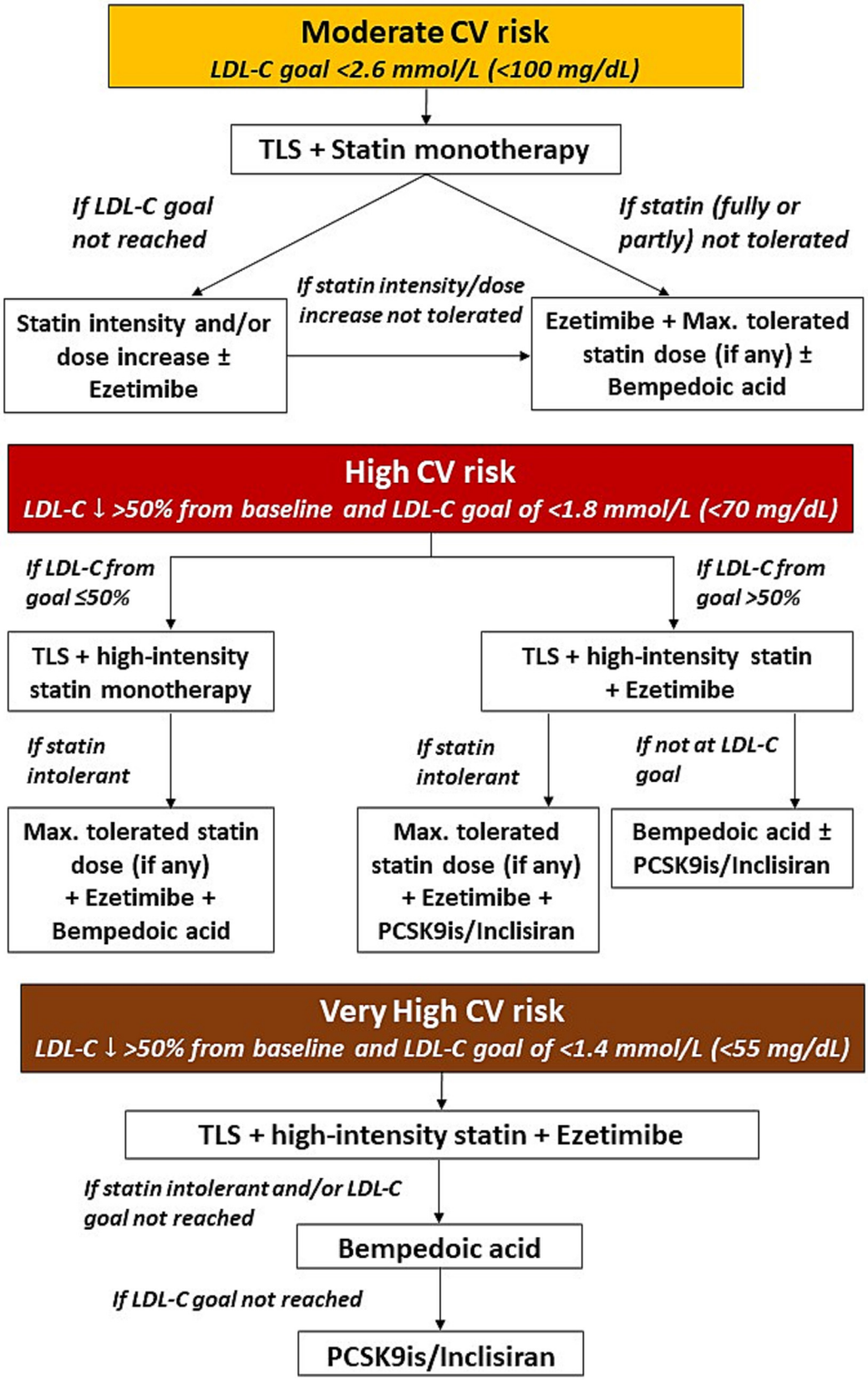

Fig. 4. Simplified flowchart for LDL-C management in clinical practice according to the estimated cardiovascular risk.
Of note, the calculation of the estimated cardiovascular risk may vary depending on the adopted score/algorithm (see text for details). In case of suspicion of homozygous familial hypercholesterolemia, directly refer to a Lipid Clinic for potential prescription of lomitapide or evinacumab.
CV: cardiovascular; LDL-C: LDL cholesterol; PCSK9is: Proprotein convertase subtilisin/kexin type 9 inhibitors (monoclonal antibodies alirocumab or evolocumab); TLS: therapeutic lifestyle.

approved by regulators with innovative mechanisms of action, including PCSK9 inhibitors (monoclonal antibodies and inclisiran), ATP-citrate lyase inhibitors (bempedoic acid), ANGPTL3 inhibitors (evinacumab), and MTP inhibitors (lomitapide). Beyond statins, these drugs share, at different extent, the ability to lower LDL-C, thus tackling the residual ASCVD risk.

Various unsettled issues remain, including the effectiveness of the upfront approach and the role of other pharmacological approaches not covered in the present review (e.g., fibrates, icosapent ethyl). Pragmatic trials (biomarker- and imaging-based) and observational evidence, including pharmacovigilance, are needed to clarify the safety and tolerability, especially in the long-term, identify subjects who benefit the most and define the place in therapy of each agent as well as the optimal sequence.

At present, PCSK9 inhibitors and bempedoic acid are gaining increasing consideration within the pharmacological armamentarium by virtue of their favorable properties such as cardiovascular benefit, frequency of administration and tolerability, which may support long-term adherence. However, cost-benefit considerations and heterogeneity in reimbursement criteria might represent limiting barriers in the local implementation.

We strongly believe on the need to effectively improve the uptake of maximally tolerated high-intensity statin and timely implementation of add-on ezetimibe as key priorities. Patient's empowerment within a multidisciplinary team coupled with proactive vigilance and engagement with general practitioners are pivotal to maximize tolerability and enhance adherence in clinical practice.

Healthcare professionals, including clinical pharmacologists, are facing an exciting era in lipid research and non-statin drugs are expected to effectively meet guidelines' expectations through a personalized approach.

Data availability

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

Declaration of Competing Interest

Emanuel Raschi and Manuela Casula declare no conflict of interest relevant to the content of this manuscript.

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References

Ahamad, S., & Bhat, S. A. (2022). Recent update on the development of PCSK9 inhibitors for hypercholesterolemia treatment. *Journal of Medicinal Chemistry 65*(23), 15513–15539. https://doi.org/10.1021/acs.jmedchem.2c01290.

Ahmad, Z., Banerjee, P., Hamon, S., Chan, K. -C., Bouzelmat, A., Sasiela, W. J., ... Dunbar, R. L. (2019). Inhibition of angiopoietin-like protein 3 with a monoclonal antibody reduces triglycerides in hypertriglyceridemia. *Circulation 140*(6), 470–486. https://doi.org/10.1161/CIRCULATIONAHA.118.039107.

Ahmad, Z., Pordy, R., Rader, D. J., Gaudet, D., Ali, S., Gonzaga-Jauregui, C., ... Dunbar, R. L. (2021). Inhibition of angiopoietin-like protein 3 with evinacumab in subjects with high and severe hypertriglyceridemia. *Journal of the American College of Cardiology 78*(2), 193–195. https://doi.org/10.1016/j.jacc.2021.04.091.

Adam, R. C., Mintah, I. J., Alexa-Braun, C. A., Shihanian, L. M., Lee, J. S., Banerjee, P., Hamon, S. C., Kim, H. I., Cohen, J. C., Hobbs, H. H., Van Hout, C., Gromada, J., Murphy, A. J., Yancopoulos, G. D., Sleeman, M. W., & Gusarova, V. (2020 Sep). Angiopoietin-like protein 3 governs LDL-cholesterol levels through endothelial lipase-dependent VLDL clearance. *J Lipid Res. 61*(9), 1271–1286. https://doi.org/10.1194/jlr.RA120000888.

Altschmiedová, T., Todorovová, V., Šnejdrlová, M., Šatný, M., & Češka, R. (2022). PCSK9 inhibitors in real-world practice: analysis of data from 314 patients and 2 years of experience in a center of preventive cardiology. *Current Atherosclerosis Reports 24*(5), 357–363. https://doi.org/10.1007/s11883-022-01008-8.

Arnett, D. K., Blumenthal, R. S., Albert, M. A., Buroker, A. B., Goldberger, Z. D., Hahn, E. J., ... Ziaeian, B. (2019). 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the american college of cardiology/american heart association task force on clinical practice guidelines. *Circulation 140*(11), e596–e646. https://doi.org/10.1161/CIR.0000000000000678.

Arnold, N., & Koenig, W. (2022). PCSK9 inhibitor wars: how does inclisiran fit in with current monoclonal antibody inhibitor therapy? Considerations for patient selection. *Current Cardiology Reports 24*(11), 1657–1667. https://doi.org/10.1007/s11886-022-01782-6.

Arnould, S., Delenda, C., Grizot, S., Desseaux, C., Pâques, F., Silva, G. H., & Smith, J. (2011). The I-CreI meganuclease and its engineered derivatives: Applications from cell modification to gene therapy. *Protein Engineering, Design & Selection: PEDS 24*(1–2), 27–31. https://doi.org/10.1093/protein/gzq083.

Attipoe-Dorcoo, S., Yang, P., Sperling, L., Loustalot, F., Thompson-Paul, A. M., Gray, E. B., ... Ritchey, M. D. (2021). Characteristics and trends of PCSK9 inhibitor prescription fills in the United States. *Journal of Clinical Lipidology 15*(2), 332–338. https://doi.org/10.1016/j.jacl.2021.01.010.

Averna, M., Banach, M., Bruckert, E., Drexel, H., Farnier, M., Gaita, D., ... Catapano, A. L. (2021). Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force. *Atherosclerosis 325*, 99–109. https://doi.org/10.1016/j.atherosclerosis.2021.03.039.

Averna, M., Bilato, C., Sesti, G., Network, I. C., & on Bempedoic Acid. (2022). Clinical evaluation of bempedoic acid for the treatment of hyperlipidaemia. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD 32*(1), 17–20. https://doi.org/10.1016/j.numecd.2021.09.023.

Bai, J., Gong, L. -L., Li, Q. -F., & Wang, Z. -H. (2018). Long-term efficacy and safety of proprotein convertase subtilisin/kexin 9 monoclonal antibodies: A meta-analysis of 11 randomized controlled trials. *Journal of Clinical Lipidology 12*(2), 277–291.e3. https://doi.org/10.1016/j.jacl.2018.01.004.

Baigent, C., Keech, A., Kearney, P. M., Blackwell, L., Buck, G., Pollicino, C., ... Simes, R. Cholesterol Treatment Trialists' (CTT) Collaborators. (2005). Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet (London, England) 366*(9493), 1267–1278. https://doi.org/10.1016/S0140-6736(05)67394-1.

Ballantyne, C. M., Banach, M., Bays, H. E., Catapano, A. L., Laufs, U., Stroes, E. S. G., ... Ray, K. K. (2022). Long-term safety and efficacy of bempedoic acid in patients with atherosclerotic cardiovascular disease and/or heterozygous familial hypercholesterolemia (from the CLEAR harmony open-label extension study). *The American Journal of Cardiology 174*, 1–11. https://doi.org/10.1016/j.amjcard.2022.03.020.

Ballantyne, C. M., Banach, M., Mancini, G. B. J., Lepor, N. E., Hanselman, J. C., Zhao, X., & Leiter, L. A. (2018). Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. *Atherosclerosis 277*, 195–203. https://doi.org/10.1016/j.atherosclerosis.2018.06.002.

Ballantyne, C. M., Banka, P., Mendez, G., Garcia, R., Rosenstock, J., Rodgers, A., ... Catapano, A. L. (2023). Phase 2b randomized trial of the oral PCSK9 inhibitor MK-0616. *Journal of the American College of Cardiology 81*(16), 1553–1564. https://doi.org/10.1016/j.jacc.2023.02.018.

Ballantyne, C. M., Bays, H., Catapano, A. L., Goldberg, A., Ray, K. K., & Saseen, J. J. (2021). Role of bempedoic acid in clinical practice. *Cardiovascular Drugs and Therapy 35*(4), 853–864. https://doi.org/10.1007/s10557-021-07147-5.

Ballantyne, C. M., Laufs, U., Ray, K. K., Leiter, L. A., Bays, H. E., Goldberg, A. C., ... Catapano, A. L. (2020). Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *European Journal of Preventive Cardiology 27*(6), 593–603. https://doi.org/10.1177/2047487319864671.

Banach, M., Burchardt, P., Chlebus, K., Dobrowolski, P., Dudek, D., Dyrbuś, K., Gąsior, M., Jankowski, P., Jóźwiak, J., Kłosiewicz-Latoszek, L., Kowalska, I., Małecki, M., Prejbisz, A., Rakowski, M., Rysz, J., Solnica, B., Sitkiewicz, D., Sygitowicz, G., Sypniewska, G., & Cybulska, B. (2021). PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021. *Archives of Medical Science: AMS 17*(6), 1447–1547. https://doi.org/10.5114/aoms/141941.

Banach, M., Cannon, C. P., Paneni, F., Penson, P. E., & endorsed by the International Lipid Expert Panel (ILEP) (2022). Individualized therapy in statin intolerance: The key to success. *European Heart Journal*, ehac556. https://doi.org/10.1093/eurheartj/ehac556.

Banach, M., Duell, P. B., Gotto, A. M., Laufs, U., Leiter, L. A., Mancini, G. B. J., ... Catapano, A. L. (2020). Association of bempedoic acid administration with atherogenic lipid levels in phase 3 randomized clinical trials of patients with hypercholesterolemia. *JAMA Cardiology 5*(10), 1124–1135. https://doi.org/10.1001/jamacardio.2020.2314.

Banach, M., Patti, A. M., Giglio, R. V., Cicero, A. F. G., Atanasov, A. G., Bajraktari, G., ... International Lipid Expert Panel (ILEP) (2018). The role of nutraceuticals in statin intolerant patients. *Journal of the American College of Cardiology 72*(1), 96–118. https://doi.org/10.1016/j.jacc.2018.04.040.

Banach, M., & Penson, P. E. (2021). Lipid-lowering therapies: Better together. *Atherosclerosis 320*, 86–88. https://doi.org/10.1016/j.atherosclerosis.2021.01.009.

Banach, M., Penson, P. E., Farnier, M., Fras, Z., Latkovskis, G., Laufs, U., ... Escobar, C. (2023). Bempedoic acid in the management of lipid disorders and cardiovascular risk. 2023 position paper of the international lipid expert panel (ILEP). *Progress in Cardiovascular Diseases S0033-0620*(23), 00026–00029. https://doi.org/10.1016/j.pcad.2023.03.001.

Banach, M., Penson, P. E., Vrablik, M., Bunc, M., Dyrbus, K., Fedacko, J., ... ACS EuroPath Central & South European Countries Project (2021). Optimal use of lipid-lowering therapy after acute coronary syndromes: A Position Paper endorsed by the International Lipid Expert Panel (ILEP). *Pharmacological Research 166*, Article 105499. https://doi.org/10.1016/j.phrs.2021.105499.

Banach, M., Reiner, Z., Cicero, A. F. G., Sabouret, P., Viigimaa, M., Sahebkar, A., ... Penson, P. E. (2022). 2022: The year in cardiovascular disease - the year of upfront lipid lowering combination therapy. *Archives of Medical Science: AMS 18*(6), 1429–1434. https://doi.org/10.5114/aoms/156147.

Banach, M., Rizzo, M., Toth, P. P., Farnier, M., Davidson, M. H., Al-Rasadi, K., ... Mikhailidis, D. P. (2015). Statin intolerance—An attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Archives of Medical Science: AMS 11*(1), 1–23. https://doi.org/10.5114/aoms.2015.49807.

Banach, M., Surma, S., Reiner, Z., Katsiki, N., Penson, P. E., Fras, Z., ... Kastelein, J. (2022). Personalized management of dyslipidemias in patients with diabetes-it is time for a new approach (2022). *Cardiovascular Diabetology 21*(1), 263. https://doi.org/10.1186/s12933-022-01684-5.

Banerjee, Y., Pantea Stoian, A., Cicero, A. F. G., Fogacci, F., Nikolic, D., Sachinidis, A., ... Rizzo, M. (2022). Inclisiran: A small interfering RNA strategy targeting PCSK9 to treat hypercholesterolemia. *Expert Opinion on Drug Safety 21*(1), 9–20. https://doi.org/10.1080/14740338.2022.1988568.

Bays, H. E., Banach, M., Catapano, A. L., Duell, P. B., Gotto, A. M., Laufs, U., ... Ballantyne, C. M. (2020). Bempedoic acid safety analysis: Pooled data from four phase 3 clinical trials. *Journal of Clinical Lipidology 14*(5), 649–659.e6. https://doi.org/10.1016/j.jacl.2020.08.009.

Benhuri, B., Ueyama, H., Takagi, H., Briasoulis, A., & Kuno, T. (2021). PCSK9 inhibitors and ezetimibe monotherapy in patients not receiving statins: A meta-analysis of randomized trials. *Current Vascular Pharmacology 19*(4), 390–397. https://doi.org/10.2174/1570161118666200807114559.

Benn, M., Nordestgaard, B. G., Frikke-Schmidt, R., & Tybjærg-Hansen, A. (2017). Low LDL cholesterol, PCSK9 and HMGCR genetic variation, and risk of Alzheimer's disease and Parkinson's disease: Mendelian randomisation study. *BMJ (Clinical Research Ed.) 357*, Article j1648. https://doi.org/10.1136/bmj.j1648.

Biolo, G., Vinci, P., Mangogna, A., Landolfo, M., Schincariol, P., Fiotti, N., ... Di Girolamo, F. G. (2022). Mechanism of action and therapeutic use of bempedoic acid in atherosclerosis and metabolic syndrome. *Frontiers in Cardiovascular Medicine 9*, 1028355. https://doi.org/10.3389/fcvm.2022.1028355.

Blaum, C., Brunner, F. J., Goßling, A., Kröger, F., Bay, B., Lorenz, T., ... Waldeyer, C. (2021). Target populations and treatment cost for bempedoic acid and PCSK9 inhibitors: a simulation study in a contemporary CAD cohort. *Clinical Therapeutics 43*(9), 1583–1600. https://doi.org/10.1016/j.clinthera.2021.07.019.

Blom, D. J., Averna, M. R., Meagher, E. A., du Toit Theron, H., Sirtori, C. R., Hegele, R. A., ... Cuchel, M. (2017). Long-term efficacy and safety of the microsomal triglyceride transfer protein inhibitor lomitapide in patients with homozygous familial hypercholesterolemia. *Circulation 136*(3), 332–335. https://doi.org/10.1161/CIRCULATIONAHA.117.028208.

Blom, D. J., Gaudet, D., Hegele, R. A., Patel, D. S., Cegla, J., Kolovou, G., & Marin, L. M. (2022). A case series assessing the effects of lomitapide on carotid intima-media thickness in adult patients with homozygous *Familial hypercholesterolaemia* in a real-world setting. *Advances in Therapy 39*(4), 1857–1870. https://doi.org/10.1007/s12325-021-02031-y.

Blom, D. J., Harada-Shiba, M., Rubba, P., Gaudet, D., Kastelein, J. J. P., Charng, M. -J., ... Rosenson, R. S. (2020). Efficacy and Safety of Alirocumab in Adults With Homozygous Familial Hypercholesterolemia: The ODYSSEY HoFH Trial. *Journal of the American College of Cardiology 76*(2), 131–142. https://doi.org/10.1016/j.jacc.2020.05.027.

Brandts, J., Dharmayat, K. I., Vallejo-Vaz, A. J., Azar Sharabiani, M. T., Jones, R., Kastelein, J. J. P., ... Ray, K. K. (2021). A meta-analysis of medications directed against PCSK9 in familial hypercholesterolemia. *Atherosclerosis 325*, 46–56. https://doi.org/10.1016/j.atherosclerosis.2021.03.042.

Bytyçi, I., Penson, P. E., Mikhailidis, D. P., Wong, N. D., Hernandez, A. V., Sahebkar, A., ... Banach, M. (2022). Prevalence of statin intolerance: A meta-analysis. *European Heart Journal 43*(34), 3213–3223. https://doi.org/10.1093/eurheartj/ehac015.

Cannon, C. P., Blazing, M. A., Giugliano, R. P., McCagg, A., White, J. A., Theroux, P., ... IMPROVE-IT Investigators (2015). Ezetimibe added to statin therapy after acute coronary syndromes. *The New England Journal of Medicine 372*(25), 2387–2397. https://doi.org/10.1056/NEJMoa1410489.

Cannon, C. P., de Lemos, J. A., Rosenson, R. S., Ballantyne, C. M., Liu, Y., Gao, Q., ... GOULD Investigators (2021). Use of lipid-lowering therapies over 2 years in GOULD, a registry of patients with atherosclerotic cardiovascular disease in the US. *JAMA Cardiology 6*(9), 1–9. https://doi.org/10.1001/jamacardio.2021.1810.

Carugo, S., Sirtori, C. R., Corsini, A., Tokgozoglu, L., & Ruscica, M. (2022). PCSK9 inhibition and risk of diabetes: Should we worry? *Current Atherosclerosis Reports 24*(12), 995–1004. https://doi.org/10.1007/s11883-022-01074-y.

Casula, M., Catapano, A. L., & Magni, P. (2022). Nutraceuticals for dyslipidaemia and glucometabolic diseases: What the guidelines tell us (and do not tell, yet). *Nutrients 14*(3), 606. https://doi.org/10.3390/nu14030606.

Casula, M., Gazzotti, M., Bonaiti, F., Olmastroni, E., Arca, M., Averna, M., ... PROSISA Study Group (2021). Reported muscle symptoms during statin treatment amongst Italian dyslipidaemic patients in the real-life setting: The PROSISA Study. *Journal of Internal Medicine 290*(1), 116–128. https://doi.org/10.1111/joim.13219.

Casula, M., Mozzanica, F., Scotti, L., Tragni, E., Pirillo, A., Corrao, G., & Catapano, A. L. (2017). Statin use and risk of new-onset diabetes: A meta-analysis of observational studies. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD 27*(5), 396–406. https://doi.org/10.1016/j.numecd.2017.03.001.

Casula, M., Olmastroni, E., Boccalari, M. T., Tragni, E., Pirillo, A., & Catapano, A. L. (2019). Cardiovascular events with PCSK9 inhibitors: An updated meta-analysis of randomised controlled trials. *Pharmacological Research 143*, 143–150. https://doi.org/10.1016/j.phrs.2019.03.021.

Baigent, C., Blackwell, L., Emberson, J., Holland, L. E., Reith, C., Bhala, N., ... Collins, R. Cholesterol Treatment Trialists' (CTT) Collaboration. (2010). Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet (London, England) 376*(9753), 1670–1681. https://doi.org/10.1016/S0140-6736(10)61350-5.

Mihaylova, B., Emberson, J., Blackwell, L., Keech, A., Simes, J., Barnes, E. H., ... Baigent, C. Cholesterol Treatment Trialists' (CTT) Collaborators. (2012). The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: Meta-analysis of individual data from 27 randomised trials. *Lancet (London, England) 380*(9841), 581–590. https://doi.org/10.1016/S0140-6736(12)60367-5.

Cholesterol Treatment Trialists' Collaboration. (2019). Efficacy and safety of statin therapy in older people: A meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet (London, England) 393*(10170), 407–415. https://doi.org/10.1016/S0140-6736(18)31942-1.

Cicero, A. F. G., Bove, M., & Borghi, C. (2018). Pharmacokinetics, pharmacodynamics and clinical efficacy of non-statin treatments for hypercholesterolemia. *Expert Opinion on Drug Metabolism & Toxicology 14*(1), 9–15. https://doi.org/10.1080/17425255.2018.1416094.

Cicero, A. F. G., Colletti, A., Bajraktari, G., Descamps, O., Djuric, D. M., Ezhov, M., ... Banach, M. (2017). Lipid-lowering nutraceuticals in clinical practice: Position paper from an International Lipid Expert Panel. *Nutrition Reviews 75*(9), 731–767. https://doi.org/10.1093/nutrit/nux047.

Cicero, A. F. G., Fogacci, F., & Cincione, I. (2021). Evaluating pharmacokinetics of bempedoic acid in the treatment of hypercholesterolemia. *Expert Opinion on Drug Metabolism & Toxicology 17*(9), 1031–1038. https://doi.org/10.1080/17425255.2021.1951222.

Cicero, A. F. G., Fogacci, F., Hernandez, A. V., & Banach, M.Lipid and Blood Pressure Meta-Analysis Collaboration (LBPMC) Group and the International Lipid Expert Panel (ILEP). (2020). Efficacy and safety of bempedoic acid for the treatment of hypercholesterolemia: A systematic review and meta-analysis. *PLoS Medicine 17*(7), Article e1003121. https://doi.org/10.1371/journal.pmed.1003121.

Cicero, A. F. G., Fogacci, F., Zambon, A., Toth, P. P., & Borghi, C. (2022). Efficacy and safety of inclisiran a newly approved FDA drug: A systematic review and pooled analysis of available clinical studies. *American Heart Journal Plus: Cardiology Research & Practice 13*. https://doi.org/10.1016/j.ahjo.2022.100127.

Cicero, A. F. G., Pontremoli, R., Fogacci, F., Viazzi, F., & Borghi, C. (2020). Effect of bempedoic acid on serum uric acid and related outcomes: a systematic review and meta-analysis of the available Phase 2 and Phase 3 clinical studies. *Drug Safety 43*(8), 727–736. https://doi.org/10.1007/s40264-020-00931-6.

Collins, R., Reith, C., Emberson, J., Armitage, J., Baigent, C., Blackwell, L., ... Peto, R. (2016). Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet (London, England) 388*(10059), 2532–2561. https://doi.org/10.1016/S0140-6736(16)31357-5.

Committee, W., Lloyd-Jones, D. M., Morris, P. B., Ballantyne, C. M., Birtcher, K. K., Covington, A. M., ... Wilkins, J. T. (2022). 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: A report of the american college of cardiology solution set oversight committee. *Journal of the American College of Cardiology 80*(14), 1366–1418. https://doi.org/10.1016/j.jacc.2022.07.006.

Corsini, A., Bellosta, S., Baetta, R., Fumagalli, R., Paoletti, R., & Bernini, F. (1999). New insights into the pharmacodynamic and pharmacokinetic properties of statins. *Pharmacology & Therapeutics 84*(3), 413–428. https://doi.org/10.1016/s0163-7258(99)00045-5.

D'Erasmo, L., Cefalù, A. B., Noto, D., Giammanco, A., Averna, M., Pintus, P., ... Sbrana, F., et al. (2017). Efficacy of lomitapide in the treatment of familial homozygous hypercholesterolemia: Results of a real-world clinical experience in Italy. *Advances in Therapy 34*(5), 1200–1210. https://doi.org/10.1007/s12325-017-0531-x.

Dayoub, E. J., Eberly, L. A., Nathan, A. S., Khatana, S. A. M., Adusumalli, S., Navar, A. M., ... Groeneveld, P. W. (2021). Adoption of PCSK9 Inhibitors Among Patients With Atherosclerotic Disease. *Journal of the American Heart Association 10*(9), Article e019331. https://doi.org/10.1161/JAHA.120.019331.

D'Erasmo, L., Giammanco, A., Suppressa, P., Pavanello, C., Iannuzzo, G., Di Costanzo, A., Tramontano, D., Minicocci, I., Bini, S., Vogt, A., Stewards, K., Roeters Van Lennep, J., Bertolini, S., Arca, M., & Italian and European Working Group on Lomitapide in HoFH (2022). Efficacy of long-term treatment of autosomal recessive hypercholesterolemia with lomitapide: A subanalysis of the pan-european lomitapide study. *Frontiers in Genetics 13*, Article 937750. https://doi.org/10.3389/fgene.2022.937750.

Derosa, G., Maffioli, P., D'Angelo, A., Girola, A., Colombo, E., Fiorenza, A. M., ... Guasti, L. (2022). Proprotein convertase subtilisin/kexin type 9 inhibitors treatment in dyslipidemic patients: A real world prescription. *Journal of Cardiovascular Medicine (Hagerstown, Md.) 23*(2), 91–97. https://doi.org/10.2459/JCM.0000000000001237.

Dewey, F. E., Gusarova, V., Dunbar, R. L., O'Dushlaine, C., Schurmann, C., Gottesman, O., ... Baras, A. (2017). Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *The New England Journal of Medicine 377*(3), 211–221. https://doi.org/10.1056/NEJMoa1612790.

Drexel, H., Coats, A. J. S., Spoletini, I., Bilato, C., Mollace, V., Perrone Filardi, P., & Rosano, G. M. C. (2020). An expert opinion paper on statin adherence and implementation of new lipid-lowering medications by the ESC Working Group on Cardiovascular Pharmacotherapy: Barriers to be overcome. *European Heart Journal. Cardiovascular Pharmacotherapy 6*(2), 115–121. https://doi.org/10.1093/ehjcvp/pvz079.

Elis, A. (2023). Current and future options in cholesterol lowering treatments. *European Journal of Internal Medicine*. https://doi.org/10.1016/j.ejim.2023.02.010 S0953-6205(23)00050-X.

Evkeeza Prescribing Information (2021). https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761181s000lbl.pdf.

Evkeeza—EPAR Product Information (2022). https://www.ema.europa.eu/en/documents/product-information/evkeeza-epar-product-information_en.pdf.

Ference, B. A., Ginsberg, H. N., Graham, I., Ray, K. K., Packard, C. J., Bruckert, E., ... Taskinen, M. -R., et al. (2017). Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *European Heart Journal 38*(32), 2459–2472. https://doi.org/10.1093/eurheartj/ehx144.

Ferraro, R. A., Leucker, T., Martin, S. S., Banach, M., Jones, S. R., & Toth, P. P. (2022). Contemporary management of dyslipidemia. *Drugs 82*(5), 559–576. https://doi.org/10.1007/s40265-022-01691-6.

Ferri, N., & Corsini, A. (2020). Clinical pharmacology of statins: An update. *Current Atherosclerosis Reports 22*(7), 26. https://doi.org/10.1007/s11883-020-00844-w.

Fogacci, F., Giovannini, M., Grandi, E., Imbalzano, E., Degli Esposti, D., Borghi, C., & Cicero, A. F. G. (2022). Management of high-risk hypercholesterolemic patients and PCSK9 inhibitors reimbursement policies: Data from a cohort of italian hypercholesterolemic outpatients. *Journal of Clinical Medicine 11*(16), 4701. https://doi.org/10.3390/jcm11164701.

Gaba, P., O'Donoghue, M. L., Park, J. -G., Wiviott, S. D., Atar, D., Kuder, J. F., ... Wang, B., et al. (2023). Association between achieved low-density lipoprotein cholesterol levels and long-term cardiovascular and safety outcomes: An analysis of FOURIER-OLE. *Circulation 147*(16), 1192–1203. https://doi.org/10.1161/CIRCULATIONAHA.122.063399.

Gargiulo, P., Basile, C., Cesaro, A., Marzano, F., Buonocore, D., Asile, G., ... Perrone-Filardi, P. (2023). Efficacy, safety, adherence and persistence of PCSK9 inhibitors in clinical practice: A single country, multicenter, observational study (AT-TARGET-IT). *Atherosclerosis 366*, 32–39. https://doi.org/10.1016/j.atherosclerosis.2023.01.001.

Gaudet, D., Gipe, D. A., Pordy, R., Ahmad, Z., Cuchel, M., Shah, P. K., ... Hovingh, G. K. (2017). ANGPTL3 inhibition in homozygous familial hypercholesterolemia. *The New England Journal of Medicine 377*(3), 296–297. https://doi.org/10.1056/NEJMc1705994.

Ge, X., Zhu, T., Zeng, H., Yu, X., Li, J., Xie, S., Wan, J., Yang, H., Huang, K., & Zhang, W. (2021). A systematic review and meta-analysis of therapeutic efficacy and safety of alirocumab and evolocumab on familial hypercholesterolemia. *BioMed Research International 2021*, 8032978. https://doi.org/10.1155/2021/8032978.

Goldberg, A. C., Leiter, L. A., Stroes, E. S. G., Baum, S. J., Hanselman, J. C., Bloedon, L. T., ... Duell, P. B. (2019). Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: The CLEAR wisdom randomized clinical trial. *JAMA 322*(18), 1780–1788. https://doi.org/10.1001/jama.2019.16585.

Goldman, A., Raschi, E., Cukierman-Yaffe, T., Dankner, R., Shouval, R., Shechter, M., ... Maor, E. (2022). Hyperglycaemic disorders associated with PCSK9 inhibitors: A real-world, pharmacovigilance study. *European Journal of Preventive Cardiology 29*(9), 1334–1342. https://doi.org/10.1093/eurjpc/zwab209.

Gouverneur, A., Sanchez-Pena, P., Veyrac, G., Salem, J. -E., Bégaud, B., & Bezin, J. (2021). Neurocognitive disorders associated with PCSK9 inhibitors: A pharmacovigilance disproportionality analysis. *Cardiovascular Drugs and Therapy*.. https://doi.org/10.1007/s10557-021-07242-7.

Grégoire, J., Champsi, S., Jobin, M., Martinez, L., Urbich, M., & Rogoza, R. M. (2022). Cost-effectiveness analysis of evolocumab in adult patients with atherosclerotic cardiovascular disease in Canada. *Advances in Therapy 39*(7), 3262–3279. https://doi.org/10.1007/s12325-022-02130-4.

Grundy, S. M., Stone, N. J., Bailey, A. L., Beam, C., Birtcher, K. K., Blumenthal, R. S., ... Yeboah, J. (2019). 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation 139*(25), e1082–e1143. https://doi.org/10.1161/CIR.0000000000000625.

Gu, J., Sanchez, R. J., Chauhan, A., Fazio, S., & Rosenson, R. S. (2022). Simulation of lipid-lowering therapy (LLT) intensification in very high-risk patients with atherosclerotic cardiovascular disease. *Journal of Clinical Lipidology 16*(6), 901–905. https://doi.org/10.1016/j.jacl.2022.10.001.

Gupta, M., Mancini, G. B. J., Wani, R. J., Ahooja, V., Bergeron, J., Manjoo, P., ... Mackinnon, E. S. (2022). Real-world insights into evolocumab use in patients with hyperlipidemia: canadian analysis from the ZERBINI study. *CJC Open 4*(6), 558–567. https://doi.org/10.1016/j.cjco.2022.03.003.

Gusarova, V., Alexa, C. A., Wang, Y., Rafique, A., Kim, J. H., Buckler, D., ... Gromada, J. (2015). ANGPTL3 blockade with a human monoclonal antibody reduces plasma lipids in dyslipidemic mice and monkeys. *Journal of Lipid Research 56*(7), 1308–1317. https://doi.org/10.1194/jlr.M054890.

Guyton, J. R., Bays, H. E., Grundy, S. M., Jacobson, T. A., & The National Lipid Association Statin Intolerance Panel, null (2014). An assessment by the Statin Intolerance Panel: 2014 update. *Journal of Clinical Lipidology 8*(3 Suppl), S72–S81. https://doi.org/10.1016/j.jacl.2014.03.002.

Hao, Q., Aertgeerts, B., Guyatt, G., Bekkering, G. E., Vandvik, P. O., Khan, S. U., ... Delvaux, N., et al. (2022). PCSK9 inhibitors and ezetimibe for the reduction of cardiovascular events: A clinical practice guideline with risk-stratified recommendations. *BMJ (Clinical Research Ed.) 377*, Article e069066. https://doi.org/10.1136/bmj-2021-069066.

Herrett, E., Williamson, E., Brack, K., Beaumont, D., Perkins, A., Thayne, A., ... StatinWISE Trial Group, et al. (2021). Statin treatment and muscle symptoms: Series of randomised, placebo controlled n-of-1 trials. *BMJ (Clinical Research Ed.) 372*, Article n135. https://doi.org/10.1136/bmj.n135.

Hong, S. -J., Lee, Y. -J., Lee, S. -J., Hong, B. -K., Kang, W. C., Lee, J. -Y., ... LODESTAR Investigators (2023). Treat-to-target or high-intensity statin in patients with coronary artery disease: A randomized clinical trial. *JAMA 329*(13), 1078–1087. https://doi.org/10.1001/jama.2023.2487.

Hooper, A. J., Burnett, J. R., & Watts, G. F. (2015). Contemporary aspects of the biology and therapeutic regulation of the microsomal triglyceride transfer protein. *Circulation Research 116*(1), 193–205. https://doi.org/10.1161/CIRCRESAHA.116.304637.

Jadhav, S. B., Crass, R. L., Chapel, S., Kerschnitzki, M., Sasiela, W. J., Emery, M. G., ... Catapano, A. L. (2022). Pharmacodynamic effect of bempedoic acid and statin combinations: Predictions from a dose-response model. *European Heart Journal. Cardiovascular Pharmacotherapy 8*(6), 578–586. https://doi.org/10.1093/ehjcvp/pvab064.

Jones, P. H., Bays, H. E., Chaudhari, U., Pordy, R., Lorenzato, C., Miller, K., & Robinson, J. G. (2016). Safety of Alirocumab (A PCSK9 Monoclonal Antibody) from 14 Randomized Trials. *The American Journal of Cardiology 118*(12), 1805–1811. https://doi.org/10.1016/j.amjcard.2016.08.072.

Juxtapid—Prescribing Information (2019). https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203858s019lbl.pdf.

Kakavand, H., Aghakouchakzadeh, M., Shahi, A., Virani, S. S., Dixon, D. L., Van Tassell, B. W., & Talasaz, A. H. (2022). A stepwise approach to prescribing novel lipid-lowering medications. *Journal of Clinical Lipidology 16*(6), 822–832. https://doi.org/10.1016/j.jacl.2022.10.003.

Kallend, D., Stoekenbroek, R., He, Y., Smith, P. F., & Wijngaard, P. (2022). Pharmacokinetics and pharmacodynamics of inclisiran, a small interfering RNA therapy, in patients with hepatic impairment. *Journal of Clinical Lipidology 16*(2), 208–219. https://doi.org/10.1016/j.jacl.2022.01.001.

Karalis, D. G., Mallya, U. G., Ghannam, A. F., Elassal, J., Gupta, R., & Boklage, S. H. (2018). Prescribing patterns of proprotein convertase subtilisin-kexin type 9 inhibitors in eligible patients with clinical atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia. *The American Journal of Cardiology 121*(10), 1155–1161. https://doi.org/10.1016/j.amjcard.2018.02.002.

Karatasakis, A., Danek, B. A., Karacsonyi, J., Rangan, B. V., Roesle, M. K., Knickelbine, T., ... Brilakis, E. S. (2017). Effect of PCSK9 inhibitors on clinical outcomes in patients with hypercholesterolemia: A meta-analysis of 35 randomized controlled trials. *Journal of the American Heart Association 6*(12), Article e006910. https://doi.org/10.1161/JAHA.117.006910.

Kasichayanula, S., Grover, A., Emery, M. G., Gibbs, M. A., Somaratne, R., Wasserman, S. M., & Gibbs, J. P. (2018). Clinical pharmacokinetics and pharmacodynamics of evolocumab, a PCSK9 inhibitor. *Clinical Pharmacokinetics 57*(7), 769–779. https://doi.org/10.1007/s40262-017-0620-7.

Katzmann, J. L., Becker, C., Bilitou, A., & Laufs, U. (2022). Simulation study on LDL cholesterol target attainment, treatment costs, and ASCVD events with bempedoic acid in patients at high and very-high cardiovascular risk. *PloS One 17*(10), Article e0276898. https://doi.org/10.1371/journal.pone.0276898.

Khoury, E., Lauzière, A., Raal, F. J., Mancini, J., & Gaudet, D. (2023). Atherosclerotic plaque regression in homozygous familial hypercholesterolaemia: A case report of a long-term lipid-lowering therapy involving LDL-receptor-independent mechanisms. *European Heart Journal. Case Reports 7*(1), ytad029. https://doi.org/10.1093/ehjcr/ytad029.

Khvorova, A. (2017). Oligonucleotide therapeutics—A new class of cholesterol-lowering drugs. *The New England Journal of Medicine 376*(1), 4–7. https://doi.org/10.1056/NEJMp1614154.

Kim, B. -K., Hong, S. -J., Lee, Y. -J., Hong, S. J., Yun, K. H., Hong, B. -K., ... RACING investigators (2022). Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): A randomised, open-label, non-inferiority trial. *Lancet (London, England) 400*(10349), 380–390. https://doi.org/10.1016/S0140-6736(22)00916-3.

Knuuti, J., Wijns, W., Saraste, A., Capodanno, D., Barbato, E., Funck-Brentano, C., ... ESC Scientific Document Group (2020). 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *European Heart Journal 41*(3), 407–477. https://doi.org/10.1093/eurheartj/ehz425.

Kolovou, G. D., Kolovou, V., Papadopoulou, A., & Watts, G. F. (2016). MTP gene variants and response to lomitapide in patients with homozygous familial hypercholesterolemia. *Journal of Atherosclerosis and Thrombosis 23*(7), 878–883. https://doi.org/10.5551/jat.34777.

Kosoglou, T., Statkevich, P., Johnson-Levonas, A. O., Paolini, J. F., Bergman, A. J., & Alton, K. B. (2005). Ezetimibe: A review of its metabolism, pharmacokinetics and drug interactions. *Clinical Pharmacokinetics 44*(5), 467–494. https://doi.org/10.2165/00003088-200544050-00002.

Krishnamurthy, A., Bradley, C., Ascunce, R., & Kim, S. M. (2022). SAMSON and the nocebo effect: management of statin intolerance. *Current Cardiology Reports 24*(9), 1101–1108. https://doi.org/10.1007/s11886-022-01729-x.

Krychtiuk, K. A., Ahrens, I., Drexel, H., Halvorsen, S., Hassager, C., Huber, K., ... Catapano, A. (2022). Acute LDL-C reduction post ACS: Strike early and strike strong: from evidence to clinical practice. A clinical consensus statement of the Association for Acute

CardioVascular Care (ACVC), in collaboration with the European Association of Preventive Cardiology (EAPC) and the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy. *European Heart Journal. Acute Cardiovascular Care 11*(12), 939–949. https://doi.org/10.1093/ehjacc/zuac123.

Lamb, Y. N. (2021). Inclisiran: First approval. *Drugs 81*(3), 389–395. https://doi.org/10.1007/s40265-021-01473-6.

Landmesser, U., Haghikia, A., Leiter, L. A., Wright, R. S., Kallend, D., Wijngaard, P., ... Ray, K. K. (2021). Effect of inclisiran, the small-interfering RNA against proprotein convertase subtilisin/kexin type 9, on platelets, immune cells, and immunological biomarkers: A pre-specified analysis from ORION-1. *Cardiovascular Research 117*(1), 284–291. https://doi.org/10.1093/cvr/cvaa077.

Laufs, U., Ballantyne, C. M., Banach, M., Bays, H., Catapano, A. L., Duell, P. B., ... Mancini, G. B. J. (2022). Efficacy and safety of bempedoic acid in patients not receiving statins in phase 3 clinical trials. *Journal of Clinical Lipidology 16*(3), 286–297. https://doi.org/10.1016/j.jacl.2022.03.001.

Laufs, U., Banach, M., Mancini, G. B. J., Gaudet, D., Bloedon, L. T., Sterling, L. R., ... Stroes, E. S. G. (2019). Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. *Journal of the American Heart Association 8*(7), Article e011662. https://doi.org/10.1161/JAHA.118.011662.

Lee, R. G., Mazzola, A. M., Braun, M. C., Platt, C., Vafai, S. B., Kathiresan, S., ... Khera, A. V. (2023). Efficacy and safety of an investigational single-course CRISPR base-editing therapy targeting PCSK9 in nonhuman primate and mouse models. *Circulation 147*(3), 242–253. https://doi.org/10.1161/CIRCULATIONAHA.122.062132.

Leipold, R., Raal, F., Ishak, J., Hovingh, K., & Phillips, H. (2017). The effect of lomitapide on cardiovascular outcome measures in homozygous familial hypercholesterolemia: A modelling analysis. *European Journal of Preventive Cardiology 24*(17), 1843–1850. https://doi.org/10.1177/2047487317730473.

Leiter, L. A., Banach, M., Catapano, A. L., Duell, P. B., Gotto, A. M., Laufs, U., ... Bays, H. E. (2022). Bempedoic acid in patients with type 2 diabetes mellitus, prediabetes, and normoglycaemia: A post hoc analysis of efficacy and glycaemic control using pooled data from phase 3 clinical trials. *Diabetes, Obesity & Metabolism 24*(5), 868–880. https://doi.org/10.1111/dom.14645.

Leqvio Prescribing Information (2021). https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214012lbl.pdf.

Leqvio—EPAR Product Information (2022). https://www.ema.europa.eu/en/documents/product-information/leqvio-epar-product-information_en.pdf.

Levin, A. A. (2017). Targeting therapeutic oligonucleotides. *The New England Journal of Medicine 376*(1), 86–88. https://doi.org/10.1056/NEJMcibr1613559.

Li, J., Du, H., Wang, Y., Aertgeerts, B., Guyatt, G., Hao, Q., ... Li, S. (2022). Safety of proprotein convertase subtilisin/kexin 9 inhibitors: A systematic review and meta-analysis. *Heart (British Cardiac Society) 108*(16), 1296–1302. https://doi.org/10.1136/heartjnl-2021-320556.

Lin, J. (2022). *Abstract 10921: Efficacy and Safety of Ongericimab in Chinese Patients With Homozygous Familial Hypercholesterolemia. VIRTUAL POSTER SESSION: REPORTS OF INTERVENTIONAL RESEARCH*. AHA.

Liu, C., Chen, J., Chen, H., Zhang, T., He, D., Luo, Q., Chi, J., Hong, Z., Liao, Y., Zhang, S., Wu, Q., Cen, H., Chen, G., Li, J., & Wang, L. (2022). PCSK9 inhibition: From current advances to evolving future. *Cells 11*(19), 2972. https://doi.org/10.3390/cells11192972.

Liu, J. (2020). *CVI-LM001, a First-in-Class Novel Oral PCSK9Modulator, Lowers Plasma Ldl-c and Reduces Circulating PCSK9 in Preclinical Animal Models and in Hyperlipidemic Human Subjects. https://doi.org/10.1161/circ.142.suppl_3.12579*.

Lojuxta—EPAR Product Information (2022). https://www.ema.europa.eu/en/documents/product-information/lojuxta-epar-product-information_en.pdf.

Lütjohann, D., Stellaard, F., Mulder, M. T., Sijbrands, E. J. G., & Weingärtner, O. (2019). The emerging concept of "individualized cholesterol-lowering therapy": A change in paradigm. *Pharmacology & Therapeutics 199*, 111–116. https://doi.org/10.1016/j.pharmthera.2019.03.004.

Mach, F., Baigent, C., Catapano, A. L., Koskinas, K. C., Casula, M., Badimon, L., ... ESC Scientific Document Group (2020). 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *European Heart Journal 41*(1), 111–188. https://doi.org/10.1093/eurheartj/ehz455.

Markham, A. (2020). Bempedoic acid: First approval. *Drugs 80*(7), 747–753. https://doi.org/10.1007/s40265-020-01308-w.

Marquina, C., Zomer, E., Vargas-Torres, S., Zoungas, S., Ofori-Asenso, R., Liew, D., & Ademi, Z. (2020). Novel treatment strategies for secondary prevention of cardiovascular disease: A systematic review of cost-effectiveness. *PharmacoEconomics 38*(10), 1095–1113. https://doi.org/10.1007/s40273-020-00936-0.

Martín-Campos, J. M., Roig, R., Mayoral, C., Martinez, S., Martí, G., Arroyo, J. A., ... Blanco-Vaca, F. (2012). Identification of a novel mutation in the ANGPTL3 gene in two families diagnosed of familial hypobetalipoproteinemia without APOB mutation. *Clinica Chimica Acta; International Journal of Clinical Chemistry 413*(5–6), 552–555. https://doi.org/10.1016/j.cca.2011.11.020.

Masana, L., Ibarretxe, D., & Plana, N. (2016). Maximum low-density lipoprotein cholesterol lowering capacity achievable with drug combinations. When 50 plus 20 equals 60. *Revista Espanola De Cardiologia (English Ed.) 69*(3), 342–343. https://doi.org/10.1016/j.rec.2015.11.014.

Masana, L., Ibarretxe, D., & Plana, N. (2020). Reasons why combination therapy should be the new standard of care to achieve the LDL-cholesterol targets: Lipid-lowering combination therapy. *Current Cardiology Reports 22*(8), 66. https://doi.org/10.1007/s11886-020-01326-w.

Minicocci, I., Montali, A., Robciuc, M. R., Quagliarini, F., Censi, V., Labbadia, G., ... Arca, M. (2012). Mutations in the ANGPTL3 gene and familial combined hypolipidemia: A clinical and biochemical characterization. *The Journal of Clinical Endocrinology and Metabolism 97*(7), E1266–E1275. https://doi.org/10.1210/jc.2012-1298.

Morrow, M. R., Batchuluun, B., Wu, J., Ahmadi, E., Leroux, J. M., Mohammadi-Shemirani, P., ... Steinberg, G. R. (2022). Inhibition of ATP-citrate lyase improves NASH, liver fibrosis, and dyslipidemia. *Cell Metabolism 34*(6), 919–936.e8. https://doi.org/10.1016/j.cmet.2022.05.004.

Mourikis, P., Zako, S., Dannenberg, L., Nia, A. M., Heinen, Y., Busch, L., ... Polzin, A. (2020). Lipid lowering therapy in cardiovascular disease: From myth to molecular reality. *Pharmacology & Therapeutics 213*, Article 107592. https://doi.org/10.1016/j.pharmthera.2020.107592.

Musunuru, K., Pirruccello, J. P., Do, R., Peloso, G. M., Guiducci, C., Sougnez, C., ... Kathiresan, S. (2010). Exome sequencing, ANGPTL3 mutations, and familial combined hypolipidemia. *The New England Journal of Medicine 363*(23), 2220–2227. https://doi.org/10.1056/NEJMoa1002926.

Nanchen, D., Carballo, D., Bilz, S., Rickli, H., Koskinas, K. C., Mach, F., ... Sudano, I. (2022). Effectiveness, adherence, and safety of evolocumab in a swiss multicenter prospective observational study. *Advances in Therapy 39*(1), 504–517. https://doi.org/10.1007/s12325-021-01962-w.

Navarese, E. P., Kolodziejczak, M., Schulze, V., Gurbel, P. A., Tantry, U., Lin, Y., ... Kelm, M. (2015). Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. *Annals of Internal Medicine 163*(1), 40–51. https://doi.org/10.7326/M14-2957.

Newman, C., Blaha, M., Boord, J., Cariou, B., Chait, A., Hg, F., ... Lr, T. (2020). Lipid management in patients with endocrine disorders: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism 105*(12). https://doi.org/10.1210/clinem/dgaa674.

NEWS RELEASE: Vaxxinity's Anti-PCSK9 Candidate Demonstrates Durable LDL Cholesterol Lowering in Non-Human Primates. https://ir.vaxxinity.com/news-releases/news-release-details/vaxxinitys-anti-pcsk9-candidate-demonstrates-durable-ldl (2022)..

NEXLETOL - Prescribing Information (2020). https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211616s000lbl.pdf.

NEXLIZET - Prescribing Information (2020). https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211617s000lbl.pdf.

Nicholls, S. J., Kataoka, Y., Nissen, S. E., Prati, F., Windecker, S., Puri, R., ... Psaltis, P. J. (2022). Effect of evolocumab on coronary plaque phenotype and burden in statin-treated patients following myocardial infarction. *JACC. Cardiovascular Imaging 15*(7), 1308–1321. https://doi.org/10.1016/j.jcmg.2022.03.002.

Nilembo—EPAR - Product Information (2022). https://www.ema.europa.eu/en/documents/product-information/nilemdo-epar-product-information_en.pdf.

Nissen, S. E., Lincoff, A. M., Brennan, D., Ray, K. K., Mason, D., Kastelein, J. J. P., ... CLEAR Outcomes Investigators (2023). Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *The New England Journal of Medicine*.. https://doi.org/10.1056/NEJMoa2215024.

Noto, D., Cefalù, A. B., Valenti, V., Fayer, F., Pinotti, E., Ditta, M., ... Averna, M. R. (2012). Prevalence of ANGPTL3 and APOB gene mutations in subjects with combined hypolipidemia. *Arteriosclerosis, Thrombosis, and Vascular Biology 32*(3), 805–809. https://doi.org/10.1161/ATVBAHA.111.238766.

Nustendi—EPAR - Product Information (2022). https://www.ema.europa.eu/en/documents/product-information/nustendi-epar-product-information_en.pdf.

O'Donoghue, M. L., Giugliano, R. P., Wiviott, S. D., Atar, D., Keech, A., Kuder, J. F., ... Sabatine, M. S. (2022). Long-term evolocumab in patients with established atherosclerotic cardiovascular disease. *Circulation 146*(15), 1109–1119. https://doi.org/10.1161/CIRCULATIONAHA.122.061620.

Pandor, A., Ara, R. M., Tumur, I., Wilkinson, A. J., Paisley, S., Duenas, A., ... Chilcott, J. (2009). Ezetimibe monotherapy for cholesterol lowering in 2,722 people: Systematic review and meta-analysis of randomized controlled trials. *Journal of Internal Medicine 265*(5), 568–580. https://doi.org/10.1111/j.1365-2796.2008.02062.x.

Parker, B. A., Capizzi, J. A., Grimaldi, A. S., Clarkson, P. M., Cole, S. M., Keadle, J., ... Thompson, P. D. (2013). Effect of statins on skeletal muscle function. *Circulation 127*(1), 96–103. https://doi.org/10.1161/CIRCULATIONAHA.112.136101.

Patti, G., Cavallari, I., Cesaro, A., Gragnano, F., Riva, L., Fimiani, F., Cuccia, C., Fresco, C., Calabrò, P., Leonardi, S., Marcucci, R., & Rubboli, A. (2022). Use of bempedoic acid for LDL cholesterol lowering and cardiovascular risk reduction: A consensus document from the Italian study group on atherosclerosis, thrombosis and vascular biology. *Vascular Pharmacology 148*, Article 107137. https://doi.org/10.1016/j.vph.2022.107137.

Penson, P. E., & Banach, M. (2021). Nocebo/drucebo effect in statin-intolerant patients: An attempt at recommendations. *European Heart Journal 42*(47), 4787–4788. https://doi.org/10.1093/eurheartj/ehab358.

Pinkosky, S. L., Newton, R. S., Day, E. A., Ford, R. J., Lhotak, S., Austin, R. C., ... Lalwani, N. D. (2016). Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nature Communications 7*, 13457. https://doi.org/10.1038/ncomms13457.

Pirillo, A., Casula, M., Olmastroni, E., Norata, G. D., & Catapano, A. L. (2021). Global epidemiology of dyslipidaemias. *Nature Reviews. Cardiology 18*(10), 689–700. https://doi.org/10.1038/s41569-021-00541-4.

Pisciotta, L., Favari, E., Magnolo, L., Simonelli, S., Adorni, M. P., Sallo, R., ... Bertolini, S. (2012). Characterization of three kindreds with familial combined hypolipidemia caused by loss-of-function mutations of ANGPTL3. *Circulation. Cardiovascular Genetics 5*(1), 42–50. https://doi.org/10.1161/CIRCGENETICS.111.960674.

Praluent Prescribing Informatrion (2021). https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125559s029s030lbl.pdf.

Praluent—EPAR Product Information (2023). https://www.ema.europa.eu/en/documents/product-information/praluent-epar-product-information_en.pdf.

Raal, F. J., Honarpour, N., Blom, D. J., Hovingh, G. K., Xu, F., Scott, R., ... TESLA Investigators (2015). Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): A randomised, double-blind, placebo-controlled trial. *Lancet (London, England) 385*(9965), 341–350. https://doi.org/10.1016/S0140-6736(14)61374-X.

Raal, F. J., Kallend, D., Ray, K. K., Turner, T., Koenig, W., Wright, R. S., ... ORION-9 Investigators (2020). Inclisiran for the treatment of heterozygous familial hypercholesterolemia. *The New England Journal of Medicine 382*(16), 1520–1530. https://doi.org/10.1056/NEJMoa1913805.

Raal, F. J., Rosenson, R. S., Reeskamp, L. F., Hovingh, G. K., Kastelein, J. J. P., Rubba, P., ... ELIPSE HoFH Investigators (2020). Evinacumab for homozygous familial hypercholesterolemia. *The New England Journal of Medicine 383*(8), 711–720. https://doi.org/10.1056/NEJMoa2004215.

Ranasinghe, P., Addison, M. L., Dear, J. W., & Webb, D. J. (2022). Small interfering RNA: Discovery, pharmacology and clinical development-An introductory review. *British Journal of Pharmacology*.. https://doi.org/10.1111/bph.15972.

Ray, K. K., Bays, H. E., Catapano, A. L., Lalwani, N. D., Bloedon, L. T., Sterling, L. R., ... Trial. (2019). Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *The New England Journal of Medicine 380*(11), 1022–1032. https://doi.org/10.1056/NEJMoa1803917.

Ray, K. K., Molemans, B., Schoonen, W. M., Giovas, P., Bray, S., Kiru, G., ... DA VINCI study (2021). EU-wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: The DA VINCI study. *European Journal of Preventive Cardiology 28*(11), 1279–1289. https://doi.org/10.1093/eurjpc/zwaa047.

Ray, K. K., Raal, F. J., Kallend, D. G., Jaros, M. J., Koenig, W., Leiter, L. A., ... III investigators (2023). Inclisiran and cardiovascular events: A patient-level analysis of phase III trials. *European Heart Journal 44*(2), 129–138. https://doi.org/10.1093/eurheartj/ehac594.

Ray, K. K., Reeskamp, L. F., Laufs, U., Banach, M., Mach, F., Tokgözoğlu, L. S., ... Kastelein, J. J. P. (2022). Combination lipid-lowering therapy as first-line strategy in very high-risk patients. *European Heart Journal 43*(8), 830–833. https://doi.org/10.1093/eurheartj/ehab718.

Ray, K. K., Troquay, R. P. T., Visseren, F. L. J., Leiter, L. A., Scott Wright, R., Vikarunnessa, S., ... Landmesser, U. (2023). Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): Results from the 4-year open-label extension of the ORION-1 trial. *The Lancet. Diabetes & Endocrinology 11*(2), 109–119. https://doi.org/10.1016/S2213-8587(22)00353-9.

Ray, K. K., Wright, R. S., Kallend, D., Koenig, W., Leiter, L. A., Raal, F. J., ... ORION-10 and ORION-11 Investigators (2020). Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *The New England Journal of Medicine 382*(16), 1507–1519. https://doi.org/10.1056/NEJMoa1912387.

Razek, O., Cermakova, L., Armani, H., Lee, T., Francis, G. A., Mancini, G. B. J., ... Brunham, L. R. (2018). Attainment of recommended lipid targets in patients with familial hypercholesterolemia: real-world experience with PCSK9 inhibitors. *The Canadian Journal of Cardiology 34*(8), 1004–1009. https://doi.org/10.1016/j.cjca.2018.04.014.

Real, J., Arbona, C., Goterris, R., & Ascaso, J. F. (2018). Management of homozygous familial hypercholesterolaemia in two brothers. *BMJ Case Reports 2018*. https://doi.org/10.1136/bcr-2017-222155 bcr2017222155, bcr-2017–222155.

Reeskamp, L. F., Nurmohamed, N. S., Bom, M. J., Planken, R. N., Driessen, R. S., van Diemen, P. A., ... Hovingh, G. K. (2021). Marked plaque regression in homozygous familial hypercholesterolemia. *Atherosclerosis 327*, 13–17. https://doi.org/10.1016/j.atherosclerosis.2021.04.014.

Repatha—EPAR Product Information (2022). https://www.ema.europa.eu/en/documents/product-information/repatha-epar-product-information_en.pdf.

Repatha—Prescribing Information (2022). https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125522s033lbl.pdf.

Ridker, P. M., Everett, B. M., Thuren, T., MacFadyen, J. G., Chang, W. H., Ballantyne, C., ... CANTOS Trial Group (2017). Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *The New England Journal of Medicine 377*(12), 1119–1131. https://doi.org/10.1056/NEJMoa1707914.

Ridker, P. M., MacFadyen, J., Libby, P., & Glynn, R. J. (2010). Relation of baseline high-sensitivity C-reactive protein level to cardiovascular outcomes with rosuvastatin in the Justification for Use of statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER). *The American Journal of Cardiology 106*(2), 204–209. https://doi.org/10.1016/j.amjcard.2010.03.018.

Robinson, J. G., Farnier, M., Krempf, M., Bergeron, J., Luc, G., Averna, M., ... ODYSSEY LONG TERM Investigators (2015). Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *The New England Journal of Medicine 372*(16), 1489–1499. https://doi.org/10.1056/NEJMoa1501031.

Rosenson, R. S., Burgess, L. J., Ebenbichler, C. F., Baum, S. J., Stroes, E. S. G., Ali, S., ... Gaudet, D. (2020). Evinacumab in Patients with Refractory Hypercholesterolemia. *The New England Journal of Medicine 383*(24), 2307–2319. https://doi.org/10.1056/NEJMoa2031049.

Roth, E. M., Goldberg, A. C., Catapano, A. L., Torri, A., Yancopoulos, G. D., Stahl, N., ... Colhoun, H. M. (2017). Antidrug antibodies in patients treated with alirocumab. *The New England Journal of Medicine 376*(16), 1589–1590. https://doi.org/10.1056/NEJMc1616623.

Ruscica, M., Banach, M., Sahebkar, A., Corsini, A., & Sirtori, C. R. (2019). ETC-1002 (Bempedoic acid) for the management of hyperlipidemia: From preclinical studies to phase 3 trials. *Expert Opinion on Pharmacotherapy 20*(7), 791–803. https://doi.org/10.1080/14656566.2019.1583209.

Ruscica, M., Corsini, A., Ferri, N., Banach, M., & Sirtori, C. R. (2020). Clinical approach to the inflammatory etiology of cardiovascular diseases. *Pharmacological Research 159*, Article 104916. https://doi.org/10.1016/j.phrs.2020.104916.

Ruscica, M., Ferri, N., Banach, M., Sirtori, C. R., & Corsini, A. (2023). Side effects of statins: From pathophysiology and epidemiology to diagnostic and therapeutic implications. *Cardiovascular Research 118*(17), 3288–3304. https://doi.org/10.1093/cvr/cvac020.

Ruscica, M., Sirtori, C. R., Carugo, S., Banach, M., & Corsini, A. (2022). Bempedoic Acid: For Whom and When. *Current Atherosclerosis Reports 24*(10), 791–801. https://doi.org/10.1007/s11883-022-01054-2.

Sabatine, M. S., Giugliano, R. P., Keech, A. C., Honarpour, N., Wiviott, S. D., Murphy, S. A., ... FOURIER Steering Committee and Investigators (2017). Evolocumab and clinical outcomes in patients with cardiovascular disease. *The New England Journal of Medicine 376*(18), 1713–1722. https://doi.org/10.1056/NEJMoa1615664.

Sabatine, M. S., Giugliano, R. P., Wiviott, S. D., Raal, F. J., Blom, D. J., Robinson, J., ... Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators (2015). Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *The New England Journal of Medicine 372*(16), 1500–1509. https://doi.org/10.1056/NEJMoa1500858.

Schachter, M. (2005). Chemical, pharmacokinetic and pharmacodynamic properties of statins: An update. *Fundamental & Clinical Pharmacology 19*(1), 117–125. https://doi.org/10.1111/j.1472-8206.2004.00299.x.

Schwartz, G. G., Steg, P. G., Szarek, M., Bhatt, D. L., Bittner, V. A., Diaz, R., ... ODYSSEY OUTCOMES Committees and Investigators (2018). Alirocumab and cardiovascular outcomes after acute coronary syndrome. *The New England Journal of Medicine 379*(22), 2097–2107. https://doi.org/10.1056/NEJMoa1801174.

Serban, M. -C., Colantonio, L. D., Manthripragada, A. D., Monda, K. L., Bittner, V. A., Banach, M., ... Rosenson, R. S. (2017). statin intolerance and risk of coronary heart events and All-cause mortality following myocardial infarction. *Journal of the American College of Cardiology 69*(11), 1386–1395. https://doi.org/10.1016/j.jacc.2016.12.036.

Silverman, M. G., Ference, B. A., Im, K., Wiviott, S. D., Giugliano, R. P., Grundy, S. M., ... Sabatine, M. S. (2016). Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: A systematic review and meta-analysis. *JAMA 316*(12), 1289–1297. https://doi.org/10.1001/jama.2016.13985.

Soffer, D., Stoekenbroek, R., & Plakogiannis, R. (2022). Small interfering ribonucleic acid for cholesterol lowering - Inclisiran: Inclisiran for cholesterol lowering. *Journal of Clinical Lipidology 16*(5), 574–582. https://doi.org/10.1016/j.jacl.2022.06.009.

Sperlongano, S., Gragnano, F., Natale, F., D'Erasmo, L., Concilio, C., Cesaro, A., Golia, E., Crisci, M., Sperlongano, R., Fimiani, F., Russo, M., Arca, M., Limongelli, G., & Calabrò, P. (2018). Lomitapide in homozygous familial hypercholesterolemia: Cardiology perspective from a single-center experience. *Journal of Cardiovascular Medicine (Hagerstown, Md.) 19*(3), 83–90. https://doi.org/10.2459/JCM.0000000000000620.

Squizzato, A., Suter, M. B., Nerone, M., Giugliano, R. P., Dentali, F., Maresca, A. M., ... Guasti, L. (2017). PCSK9 inhibitors for treating dyslipidemia in patients at different cardiovascular risk: A systematic review and a meta-analysis. *Internal and Emergency Medicine 12*(7), 1043–1053. https://doi.org/10.1007/s11739-017-1708-7.

Stefanutti, C. (2020). Lomitapide-a microsomal triglyceride transfer protein inhibitor for homozygous familial hypercholesterolemia. *Current Atherosclerosis Reports 22*(8), 38. https://doi.org/10.1007/s11883-020-00858-4.

Stefanutti, C., Chan, D. C., Di Giacomo, S., Morozzi, C., & Watts, G. F. (2022). Long-term efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia: Real-world clinical experience. *Pharmaceuticals (Basel, Switzerland) 15*(11), 1389. https://doi.org/10.3390/ph15111389.

Stefanutti, C., Morozzi, C., Di Giacomo, S., Sovrano, B., Mesce, D., & Grossi, A. (2016). Management of homozygous familial hypercholesterolemia in real-world clinical practice: A report of 7 Italian patients treated in Rome with lomitapide and lipoprotein apheresis. *Journal of Clinical Lipidology 10*(4), 782–789. https://doi.org/10.1016/j.jacl.2016.02.009.

Stein, E. A. (2014). *LDL CHOLESTEROL REDUCTION WITH BMS-962476, AN ADNECTIN INHIBITOR OF PCSK9: RESULTS OF A SINGLE ASCENDING DOSE STUDY63*..

Stitziel, N. O., Khera, A. V., Wang, X., Bierhals, A. J., Vourakis, A. C., Sperry, A. E., ... PROMIS and Myocardial Infarction Genetics Consortium Investigators (2017). ANGPTL3 deficiency and protection against coronary artery disease. *Journal of the American College of Cardiology 69*(16), 2054–2063. https://doi.org/10.1016/j.jacc.2017.02.030.

Stoekenbroek, R. M., Lambert, G., Cariou, B., & Hovingh, G. K. (2018). Inhibiting PCSK9—biology beyond LDL control. *Nature Reviews. Endocrinology 15*(1), 52–62. https://doi.org/10.1038/s41574-018-0110-5.

Strilchuk, L., Fogacci, F., & Cicero, A. F. (2019). Safety and tolerability of injectable lipid-lowering drugs: An update of clinical data. *Expert Opinion on Drug Safety 18*(7), 611–621. https://doi.org/10.1080/14740338.2019.1620730.

Stroes, E. S., Thompson, P. D., Corsini, A., Vladutiu, G. D., Raal, F. J., Ray, K. K., ... European Atherosclerosis Society Consensus Panel (2015). Statin-associated muscle symptoms: Impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *European Heart Journal 36*(17), 1012–1022. https://doi.org/10.1093/eurheartj/ehv043.

Tikka, A., & Jauhiainen, M. (2016). The role of ANGPTL3 in controlling lipoprotein metabolism. *Endocrine 52*(2), 187–193. https://doi.org/10.1007/s12020-015-0838-9.

Tombling, B. J., Zhang, Y., Huang, Y. -H., Craik, D. J., & Wang, C. K. (2021). The emerging landscape of peptide-based inhibitors of PCSK9. *Atherosclerosis 330*, 52–60. https://doi.org/10.1016/j.atherosclerosis.2021.06.903.

Toth, P. P., Worthy, G., Gandra, S. R., Sattar, N., Bray, S., Cheng, L. -I., ... Stroes, E. S. G. (2017). Systematic review and network meta-analysis on the efficacy of evolocumab and other therapies for the management of lipid levels in hyperlipidemia. *Journal of the American Heart Association 6*(10), Article e005367. https://doi.org/10.1161/JAHA.116.005367.

Tucker, T. J., Embrey, M. W., Alleyne, C., Amin, R. P., Bass, A., Bhatt, B., ... Walji, A. (2021). A series of novel, highly potent, and orally bioavailable next-generation tricyclic peptide PCSK9 inhibitors. *Journal of Medicinal Chemistry 64*(22), 16770–16800. https://doi.org/10.1021/acs.jmedchem.1c01599.

Turner, T. A. (2020). *Results of a 52 week open-label phase 2B study to assess long-term safety, immunogenicity and LDL-C efficacy of monthly dosing with LIB003 a novel anti-PCSK9 recombinant fusion protein315*.. *https://doi.org/10.1016/j.atherosclerosis.2020.10.039*.

Underberg, J. A., Cannon, C. P., Larrey, D., Makris, L., Blom, D., & Phillips, H. (2020). Long-term safety and efficacy of lomitapide in patients with homozygous familial hypercholesterolemia: Five-year data from the Lomitapide Observational Worldwide

Evaluation Registry (LOWER). *Journal of Clinical Lipidology 14*(6), 807–817. https://doi.org/10.1016/j.jacl.2020.08.006.

Visseren, F. L. J., Mach, F., Smulders, Y. M., Carballo, D., Koskinas, K. C., Bäck, M., ... ESC Scientific Document Group (2021). 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *European Heart Journal 42*(34), 3227–3337. https://doi.org/10.1093/eurheartj/ehab484.

Volpe, M., & Patrono, C. (2023). Bempedoic acid: A CLEAR therapeutic option for statin-intolerant patients? *European Heart Journal ehad206*. https://doi.org/10.1093/eurheartj/ehad206.

Warden, B. A., Cardiology, B. -A., Purnell, J. Q., Duell, P. B., & Fazio, S. (2022). Real-world utilization of bempedoic acid in an academic preventive cardiology practice. *Journal of Clinical Lipidology 16*(1), 94–103. https://doi.org/10.1016/j.jacl.2021.11.013.

Wright, R. S., Collins, M. G., Stoekenbroek, R. M., Robson, R., Wijngaard, P. L. J., Landmesser, U., ... Kallend, D. (2020). Effects of renal impairment on the pharmacokinetics, efficacy, and safety of inclisiran: An analysis of the ORION-7 and ORION-1 studies. *Mayo Clinic Proceedings 95*(1), 77–89. https://doi.org/10.1016/j.mayocp.2019.08.021.

Zeitlinger, M., Bauer, M., Reindl-Schwaighofer, R., Stoekenbroek, R. M., Lambert, G., Berger-Sieczkowski, E., ... Staffler, G. (2021). A phase I study assessing the safety, tolerability, immunogenicity, and low-density lipoprotein cholesterol-lowering activity of immunotherapeutics targeting PCSK9. *European Journal of Clinical Pharmacology 77*(10), 1473–1484. https://doi.org/10.1007/s00228-021-03149-2.

Zhang, X. -L., Zhu, Q. -Q., Zhu, L., Chen, J. -Z., Chen, Q. -H., Li, G. -N., Xie, J., Kang, L. -N., & Xu, B. (2015). Safety and efficacy of anti-PCSK9 antibodies: A meta-analysis of 25 randomized, controlled trials. *BMC Medicine 13*, 123. https://doi.org/10.1186/s12916-015-0358-8.