Drugs for dyslipidaemia: the legacy effect of the Scandinavian Simvastatin Survival Study (4S)

Timo E Strandberg, Petri T Kovanen, Donald M Lloyd-Jones, Frederick J Raal, Raul D Santos, Gerald F Watts

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University of Helsinki and Helsinki University Hospital, Helsinki, Finland (Prof T E Strandberg MD PhD); **University of Oulu, Center for Life Course Health Research, Oulu, Finland** (Prof T E Strandberg); **Wihuri Research Institute, Helsinki, Finland** (Prof P T Kovanen MD PhD); **Department of Preventive Medicine and Department of Medicine (Cardiology), Northwestern University Feinberg School of Medicine, Chicago, IL, USA** (Prof D M Lloyd-Jones MD PhD); **Division of Endocrinology and Metabolism, University of the Witwatersrand, Johannesburg, South Africa** (Prof F J Raal MD PhD); **Academic Research Organization, Hospital Israelita Albert Einstein, São Paulo, Brazil** (Prof R D Santos MD PhD); **Lipid Clinic Heart Institute (InCor) University of São Paulo Medical School Hospital, São Paulo, Brazil** (Prof R D Santos); **School of Medicine, University of Western Australia, Perth, WA, Australia** (Prof G F Watts DSc DM); **Cardiometabolic Service, Department of Cardiology and Internal Medicine, Royal Perth Hospital, Perth, WA, Australia** (Prof G F Watts)

Correspondence to: Prof Timo E Strandberg, University of Helsinki and Helsinki University Hospital, Helsinki 00029 HUS, Finland **timo.strandberg@helsinki.fi**

See Online for appendix

Since the discovery of statins and the Scandinavian Simvastatin Survival Study (4S) results three decades ago, remarkable advances have been made in the treatment of dyslipidaemia, a major risk factor for atherosclerotic cardiovascular disease. Safe and effective statins remain the cornerstone of therapeutic approach for this indication, including for children with genetic dyslipidaemia, and are one of the most widely prescribed drugs in the world. However, despite the affordability of generic statins, they remain underutilised worldwide. The use of ezetimibe to further decrease plasma LDL cholesterol and the targeting of other atherogenic lipoproteins, such as triglyceride-rich lipoproteins and lipoprotein(a), are likely to be required to further reduce atherosclerotic cardiovascular disease events. Drugs directed at these lipoproteins, including gene silencing and editing methods that durably suppress the production of proteins, such as PCSK9 and ANGPTL3, open novel therapeutic options to further reduce the development of atherosclerotic cardiovascular disease.

Introduction

November, 2024, marks the 30th anniversary of the Scandinavian Simvastatin Survival Study (4S).[1] This clinical trial was the first to show that cholesterol-lowering treatment with a statin reduced the incidence of atherosclerotic cardiovascular disease and saved lives by reducing all-cause mortality by 30% (appendix p 1). Led by the Norwegian cardiologist Terje Pedersen,[2] the study revolutionised atherosclerotic cardiovascular disease prevention, and it should have finally ended the so-called cholesterol wars—one of the major controversies of modern medicine to date at the time.[3] The idea that cholesterol accumulation causes atherosclerosis was posited over a century ago, but it was not until the Framingham Heart Study report that high cholesterol was reidentified as a key risk factor.[4] Drug treatment of dyslipidaemia in the clinic was uncommon before the 4S; cholestyramine, clofibrate, and medical procedures, such as ileal bypass and plasmapheresis, were used for the most severe cases, such as homozygous and heterozygous familial hypercholesterolaemia. The main reason for the poor results of older dyslipidaemia drugs was their modest reduction of plasma LDL cholesterol and the associated adverse events.

Search strategy and selection criteria

In addition to personal libraries of the authors, data for this Therapeutics article were identified by searches of MEDLINE, PubMed, Cochrane Library, ClinicalTrials.gov, and references from relevant articles, using the search terms "dyslipidemia drug(s)", "lipid-lowering drug(s)", "cholesterol drug(s)", "PCSK9 inhibition", "apo(a)" inhibition, "apo(a) inhibition, "ANGPTL* inhibition" and "ApoCIII inhibition". Articles published from database inception up to July 31, 2024, were included. Given space limitations and the large number of publications found, inclusion of reports during the last 5 years was prioritised.

Two discoveries were particularly impactful for the field: first, the Nobel Prize-winning recognition of the LDL receptor (LDLR) as the prime regulator of cellular cholesterol metabolism;[5] and second, the great efforts by Akira Endo and colleagues Akira Yamamoto and Hiroshi Mabuchi, which led to the discovery of statins.[6] Inspired by Alexander Fleming's discovery of penicillin, Endo had studied 6000 moulds for their ability to prevent the cellular synthesis of cholesterol. In 1973, he found a cholesterol synthesis-inhibiting compound named compactin, produced by *Penicillium citrinum*. Mechanistically, inhibition of hepatic cholesterol synthesis lowered plasma LDL cholesterol by stimulating hepatic LDLR upregulation and, consequently, increased clearance of circulating LDL particles. The discovery of compactin (or mevastatin) was a forerunner to the development of more effective statins that, after 4S, drastically transformed the prevention of atherosclerotic cardiovascular disease and became one of the most widely used drugs worldwide.[3,7–9]

However, statins were neither the first nor the last class of drugs used to treat dyslipidaemia (appendix pp 2–9). To further lower LDL cholesterol and other atherogenic lipoproteins beyond what is achievable with statins, a new wave in the treatment of dyslipidaemias has emerged. In acknowledgment of the 30th anniversary of 4S, this Therapeutics piece focuses on drug therapies for dyslipidaemias, aiming to review their role, limitations, challenges, and new opportunities.

Definition, global prevalence, and significance of dyslipidaemias

Phenotypically, dyslipidaemias are defined as disordered lipid and lipoprotein metabolism characterised by high concentrations of plasma triglycerides, lipoprotein(a), or LDL cholesterol, or by low concentrations of HDL cholesterol, which might each occur isolated or as part of combined hyperlipidaemia. Dyslipidaemias are molecularly heterogeneous, ranging from relatively uncommon monogenic forms (eg, familial hypercholesterolaemia) to

common, complex polygenic conditions, and can be further divided into primary and secondary types (eg, due to hypothyroidism or to diabetes and obesity). Dyslipidaemias typically result from kinetic perturbations in circulating lipoproteins (ie, due to overproduction, low catabolism, or both); the fundamental aim of pharmacotherapies is to correct these defects.[10,11]

Whatever the underlying mechanism, dyslipidaemias are an important risk factor for atherosclerotic cardiovascular disease. In 2019, 3·78 million ischaemic heart disease deaths were attributed to hypercholesterolaemia.[12] Ischaemic heart disease deaths attributed to hypercholesterolaemia occur both in high-income countries (HICs), mostly driven by the obesity epidemic predisposing individuals to metabolic syndrome[13] and ageing, and in low-income and medium-income countries (LMICs), where suboptimal therapy further contributes to ever-increasing rates of atherosclerotic cardiovascular disease. The prevalence of dyslipidaemia is extremely low in Indigenous populations[14] and in populations in extreme poverty,[15] but prevalence increases with age and in those of low socioeconomic status. Previously, dyslipidaemia-related risk was high in HICs and low in LMICs; however, over the past 40 years, societal changes (eg, diet quality, lifestyle) have resulted in an inverse pattern (ie, reduced risk in HICs and increased risk in LMICs). The transition is especially noticeable for non-HDL cholesterol,[16] which reflects the total burden of atherosclerotic lipoproteins. Underlying genetic dyslipidaemias are influenced by an inactive, obesity-promoting lifestyle that has various harmful effects on lipid metabolism, a feature that is also pertinent to familial hypercholesterolaemia—a condition with which a child is born every minute, and which affects one in 310 individuals worldwide.[17]

Although LDL cholesterol is a proven cause and currently the most important target of lipid-lowering therapy,[3,8] other types of dyslipidaemias can also increase atherosclerotic cardiovascular disease risk. Hypertriglyceridaemia might affect 25% or more of the population in countries with rising rates of obesity.[18] Elevated lipoprotein(a), which is due to genetic causes and affects 20% of the global population, further increases the risk of atherosclerotic cardiovascular disease.[19] Consequently, LMICs are facing a double dilemma: unhealthy lifestyle and a diet increasingly high in processed foods, fat, sugar, and salt popularised in HICs, predisposing individuals to obesity and dyslipidaemia; and ageing populations, with an increased cumulative burden of cholesterol. Furthermore, identification and treatment of dyslipidaemias are often suboptimal, and even low-cost generic statins might not be available or affordable in LMICs.

Drug therapy focusing on LDL cholesterol

Current guidelines to prevent atherosclerotic cardiovascular disease focus on lowering LDL cholesterol and recommend goals and thresholds to consider additional treatments according to atherosclerotic cardiovascular disease risk, with more intensive LDL cholesterol lowering recommended for individuals at high risk. International examples are shown in panel 1.[20–22] Most guidelines also offer secondary therapy goals, including lowering non-HDL cholesterol, apolipoprotein B, or triglycerides.

The drugs shown to be most effective in lowering risk of atherosclerotic cardiovascular disease in outcome trials, including statins, monoclonal PCSK9 inhibitors, ezetimibe, bempedoic acid, and even bile acid sequestrants, act by upregulating hepatic LDLRs and

***Panel 1*: Comparison of current international lipid guidelines for prevention of atherosclerotic cardiovascular disease**

European Society of Cardiology and European Atherosclerosis Society[20] LDL cholesterol concentration goals:

- Moderate atherosclerotic cardiovascular disease risk: <2·6 mmol/L (100 mg/dL)
- High atherosclerotic cardiovascular disease risk: <1·8 mmol/L (70 mg/dL)
- Very high atherosclerotic cardiovascular disease risk or very high risk in primary prevention: <1·4 mmol/L (55 mg/dL)

Japan Atherosclerosis Society[21] LDL cholesterol concentration goals:

- Primary prevention, low atherosclerotic cardiovascular disease risk: <4·1 mmol/L (160 mg/dL)
- Primary prevention, moderate atherosclerotic cardiovascular disease risk: <3·6 mmol/L (140 mg/dL)
- Primary prevention, high atherosclerotic cardiovascular disease risk: <3·1 mmol/L (120 mg/dL)
- Secondary prevention: <2·6 mmol/L (100 mg/dL); if high-risk conditions, such as acute coronary syndrome, familial hypercholesterolaemia, or diabetes are present: <1·8 mmol/L (70 mg/dL)

American Heart Association and American College of Cardiology[22] LDL cholesterol concentration thresholds for consideration of additional therapy:

- Primary prevention, very high LDL cholesterol >4·9 mmol/L (190 mg/dL): despite maximally tolerated statin, LDL-cholesterol is reduced <50% or remains >2·6 mmol/L (100 mg/dL), or both
- Primary prevention, diabetes: despite maximally tolerated statin, LDL-cholesterol is reduced <50%
- Primary prevention, intermediate risk: despite maximally tolerated statin, LDL-cholesterol is reduced <30%
- Primary prevention, high risk: despite maximally tolerated statin, LDL-cholesterol is reduced <50%
- Secondary prevention: despite maximally tolerated statin, LDL cholesterol is reduced <50% and remains >1·8 mmol/L (70 mg/dL)

reducing LDL cholesterol.[8,23] Lowering other atherogenic lipoproteins is also recommended, but evidence supporting such interventions is weaker than that for LDL cholesterol reductions.[19,20,24,25] Enthusiasm for increasing HDL cholesterol levels has waned given the evolving evidence (as will be discussed later), and HDL cholesterol has been relegated to a risk marker of atherosclerotic cardiovascular disease.

Currently, generic statins are the most used therapy for elevated LDL cholesterol concentrations (and also for moderate hypertriglyceridaemia), and their low cost facilitates their use, especially in LMICs. Given that socioeconomic inequalities are associated with increased cardiovascular risk, expansion of statins use in LMICs might help to mitigate that risk.[26] Seven statins are currently in clinical use: lovastatin, simvastatin, pravastatin, fluvastatin, pitavastatin (not globally available), atorvastatin, and rosuvastatin;[9] with the last two being called high-potency statins. Meta-analyses of large statin randomised clinical trials have shown the efficacy and safety of statins in reducing atherosclerotic cardiovascular disease events, both in primary and secondary prevention, including in several subgroups (eg, individuals older than 65 years, various ethnic groups, and individuals with diabetes or other comorbidities and various levels of untreated LDL cholesterol concentrations).[27,28] Moreover, efficacy and safety have been observed in children with familial hypercholesterolaemia,[29,30] as well as in patients with particular conditions, such as after heart transplantation or individuals living with HIV.[31]

The Cholesterol Treatment Trialists Collaboration studies have indicated that the greater the reduction in LDL cholesterol, the greater the relative atherosclerotic cardiovascular disease risk reduction.[27,28] Absolute risk reduction, in turn, is related to baseline LDL cholesterol level, total atherosclerotic cardiovascular disease risk, and duration of treatment. Therefore, not just the reduction of plasma LDL cholesterol but also early initiation of therapy and long-term use in individuals at risk (ie, reducing so-called cholesterol-years) all contribute to best outcomes.

Data from randomised controlled trials including primary prevention in individuals older than 75 years are insufficient,[28] although subgroup analyses and observational data suggest that the benefit of statins is not dependent on age.[32] Two large, placebo-controlled, primary prevention trials with atorvastatin 40 mg and participants older than 70–75 years at baseline (STAREE[33] and PREVENTABLE[34]) are ongoing, with results expected in 2026; such trials will also include new outcomes, such as cognitive and physical function and disability.

Risk stratification and optimisation of therapy

Although atherosclerotic cardiovascular disease is prevalent in both HICs and LMICs, not all individuals benefit meaningfully from LDL cholesterol lowering as primary prevention. However, with accumulating evidence, the LDL cholesterol threshold for initiation of drug treatment has progressively decreased.[20,22] Common risk calculators, such as SCORE2, SCORE2-OP,[20] the American College of Cardiology and American Heart Association's risk estimator,[22] and the new PREVENT risk calculator[35] all have limitations. First, these calculators rely on traditional risk factors and other risk-enhancing biomarkers (eg, coronary artery calcium) to refine individual patient risk,[20] but such biomarkers are often not commonly affordable in LMICs. Second, these calculators provide estimations over a short timeframe (not a lifetime). Third, risk prediction is primarily based on data from White populations in HICs or multi-ethnic populations in the USA.

The main reason for residual risk in secondary prevention (ie, risk remaining despite standard therapy with a statin) is probably that effective treatment has been initiated too late or in suboptimal doses to prevent progression or to allow the stabilisation of complex atherosclerotic lesions.[3] Residual risk might be mitigated by achieving very low (<1·4 mmol/L) LDL cholesterol concentrations (usually requiring drug combinations)[36] and controlling inflammation.[37] Evidence on the benefit of lowering other atherogenic lipid fractions, such as triglyceride remnants and high lipoprotein(a), is not yet conclusive.

Combinations of statins and other therapies, such as ezetimibe or monoclonal PCSK9 inhibitors, can reduce the residual risk of atherosclerotic cardiovascular disease,[38–40] but are expensive (except for ezetimibe) and their usage is low, even in HICs. A solution is to initiate a low-cost combination of a statin plus ezetimibe earlier—even before age 40 years—in individuals at high lifetime risk to reduce the LDL cholesterol burden. For young people, increased lifetime risk is a better indicator of prognosis than 10-year absolute risk. Substantially slowing or even arresting atherosclerosis is easier to do at an early stage, before it is established.[3,29]

Statins might be less effective in individuals who are high absorbers of dietary cholesterol,[41] but routine methods to identify these individuals are currently unavailable, and adding ezetimibe is a practical solution to improve the efficacy of statins. Gut microbiome–statin bidirectional interactions are an interesting area of research,[42,43] but the clinical value of promoting cardiovascular risk reduction remains unclear. Statins are generally safe, and their low rates of adverse effects have been well established for decades.[9,27,28,44]

Current and emerging non-atherosclerotic cardiovascular disease indications for statins

Repurposing statins for other indications in addition to atherosclerotic cardiovascular disease is a hot topic. Statins have both anti-inflammatory and antithrombotic effects, and inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase also affects intermediates in the cholesterol biosynthetic pathway, which are important

for cell metabolism and growth. Robust evidence has shown that the reduction of atherosclerotic cardiovascular disease by statins is predominantly due to reductions in plasma LDL cholesterol,[45] but cholesterol toxicity might also be involved in multiple non-atherosclerotic cardiovascular disease conditions,[46] for which the pleiotropic effects of statins might be beneficial. A systematic review of such effects is beyond the scope of this Therapeutics article, but various non-atherosclerotic cardiovascular disease conditions that might benefit from statin therapy are shown in table 1.[20,47–55]

Non-statin therapies

Directed at lowering LDL cholesterol

Reduction in LDL cholesterol leads to improved clinical outcomes, regardless of the mechanism of reduction.[23,36,56] Although the absolute benefit decreases, the relative risk reduction for major atherosclerotic cardiovascular disease is consistent and proportional to a decrease in LDL cholesterol—even in patients who have LDL cholesterol (before initiation or intensification of therapy) as low as 1·6 mmol/L (62 mg/dL), which then falls to less than 0·5 mmol/L (19 mg/dL) with treatment.[36] These LDL cholesterol concentrations are usually not achieved with statin therapy alone, and combination therapy is required.

Atherosclerotic cardiovascular disease reduction has been achieved in dietary trials,[3] and having a healthy lifestyle alongside drug therapy is certainly important.[57] Although a focus on non-drug therapies is beyond the purpose of this Therapeutics article, it is worth noting that nutraceuticals (eg, plant sterols) can reduce cholesterol absorption and plasma LDL cholesterol modestly,[58] although dedicated outcome studies are lacking.

Dietary cholesterol absorption and reabsorption of biliary cholesterol substantially contribute to plasma LDL cholesterol levels.[41] This finding underscores the value of dual action on cholesterol balance—ie, inhibiting absorption by blocking NPC1L1 (with ezetimibe) and inhibiting hepatic synthesis (with a statin). Ezetimibe alone can reduce plasma LDL cholesterol by 13–20%, but more effective reduction can be reached with statin plus ezetimibe combination therapies.[59,60]

In addition to statins, another inhibitor of cholesterol synthesis is bempedoic acid, an ATP citrate lyase inhibitor that also indirectly upregulates hepatic LDLR expression.[61] Bempedoic acid is a pro-drug that is mainly activated in the liver, decreasing the risk of muscle adverse events. Bempedoic acid can be combined with other drugs (eg, ezetimibe or a statin), or it can be used as monotherapy in patients with statin intolerance.[62]

An efficient mechanism for upregulation of hepatic LDLR activity, even with statin therapy, is the inhibition of PCSK9 protein interaction with LDLR on the hepatocyte surface.[63] Loss-of-function variants leading to reduced synthesis of PCSK9 were discovered in 2005, and because individuals with these variants have lifelong low LDL cholesterol levels, their lifetime risk of atherosclerotic cardiovascular disease is low, even in the presence of other atherosclerotic cardiovascular disease risk factors. LDL cholesterol concentrations of less than

	Observational studies	Specific randomised controlled trials	Notes
Diabetes	Statins shown to be beneficial	Statins shown to be beneficial	Several randomised controlled trials[20]
Deep vein thrombosis	Statins shown to be beneficial	Statins shown to be beneficial	Several randomised controlled trials[47]
Metabolic dysfunction-associated steatotic liver disease	Statins shown to be beneficial	Statins improved biochemical risk factors of atherosclerotic cardiovascular disease	No specific randomised controlled trials with clinical outcomes[48]
Infections	Statins improved prognosis in studies of influenza, pneumonia, COVID-19, etc	No evidence of benefit with de novo statin treatment observed	Chronic use might protect the host by reducing possible atherosclerotic cardiovascular disease complications[49,50,51]
Cancer	Statins showed inconsistent results in various cancer types	Not available	Although specific anticancer effects of statins are unclear, reduction of atherosclerotic cardiovascular disease complications in patients with cancer is a plausible effect[52]
Osteoporosis and fractures	Statins shown to be beneficial	Statins shown to be beneficial	Potential for decreased risk of fractures and increased bone mass density[53]
Cognitive disorders and dementia	Statins shown to be beneficial or neutral	No effects for secondary prevention in patients with Alzheimer's disease; primary prevention trials are ongoing	Potential beneficial mechanisms include prevention of ischaemic strokes (which predispose to cognitive disorders) and prevention of atherosclerotic cardiovascular disease complications in patients with dementia; high LDL cholesterol has been recognised as a risk factor of dementia by the *Lancet* standing Commission on dementia[54]
Idiopathic pulmonary fibrosis	Statins provided inconsistent benefit	No studies	Antifibrotic effect, potentially favourable[55]

Table 1: **Effects of statins on selected non-atherosclerotic cardiovascular disease conditions**

0·5 mmol/L (19 mg/dL) have been described in these individuals with no negative clinical effects.[63,64] These discoveries led to the rapid development of PCSK9 inhibitors, first as monoclonal antibodies (evolocumab, alirocumab, and lerodalcibep [NCT04806893] and recaticimab [NCT04849000], which are still under development), and thereafter as small interfering RNAs (siRNAs), such as inclisiran, which inhibit hepatic PCSK9 synthesis.[65] Subcutaneous treatment administration on a twice monthly or monthly basis (for the antibodies), or even twice annually (for inclisiran), is likely to improve adherence to the lifelong lipid-lowering treatment. Oral PCSK9 inhibitors have also been studied,[66,67] including MK-0616 in an ongoing phase 3 outcome study (NCT06008756).

Overall, treatments with PCSK9-directed therapies have reduced LDL cholesterol levels by 50–60%. The trials with PCSK9 inhibitors have mainly involved patients receiving statin therapy, but PCSK9 inhibitors alone can also effectively lower LDL cholesterol levels in patients with statin intolerance.[68] In addition to adults, PCSK9 inhibitor therapies have also been studied in children with familial hypercholesterolaemia and found to be safe.[69,70] The high cost of these treatments currently prevents widespread use even in HICs, but PCSK9 inhibitors have the potential to be cost-effective in secondary prevention for patients at the highest risk.[71]

Directed at triglycerides and triglyceride-rich lipoproteins

Whether high triglycerides cause atherosclerotic cardiovascular disease remains uncertain, and therefore, triglycerides have been a controversial treatment target.[24] Trial evidence in the pre-statin era showed that the triglyceride-lowering agents clofibrate and gemfibrozil could reduce coronary events,[3] but no consistent evidence that triglycerides per se promote atherosclerosis exist.[72] A more plausible mechanism is that the cholesterol in triglyceride-rich lipoprotein remnants (eg, VLDL, intermediate-density lipoprotein, and chylomicron remnants) accumulates in atherosclerotic lesions,[73] and evidence also indicates that triglyceride-rich lipid droplets are pro-inflammatory.[74–76] In practice, elevated triglyceride concentrations should be considered indicators of altered metabolism of pro-atherogenic triglyceride-rich apolipoprotein B-containing remnant lipoproteins. This view is supported by a large mendelian randomisation study[77] that showed a causal association between remnant cholesterol and atherosclerotic cardiovascular disease outcomes. Elevated triglyceride-rich lipoprotein particles, particularly remnant lipoproteins, and low-grade arterial inflammation might synergistically alter the progression of atherosclerotic cardiovascular disease.[78] Estimating remnant cholesterol and measuring high-sensitivity C-reactive protein might be useful to quantify residual risk in patients with LDL cholesterol treated to goal.[78] This notion merits further investigation.

The potential value of the triglyceride-lowering effect of fibrates attracted much attention for decades, being especially relevant in the context of diabetes and the metabolic syndrome. Fibrates are agonists of the peroxisome proliferator-responsive receptor-α (PPARA-α), a nuclear transcription factor; the activation of PPARA-α decreases hepatic secretion of apoC3, promoting plasma triglyceride clearance. Fibrates also increase the expression of apolipoprotein A-I and apolipoprotein A-II, leading to elevation in plasma HDL cholesterol concentrations,[79] although the effect on LDL cholesterol and total apolipoprotein B is modest. Fenofibrate is more selective for PPAR-α, whereas bezafibrate is a pan-agonist for PPAR-α, β, and δ. A more recently developed drug in this class, pemafibrate, is a selective PPAR-α modulator that results in an increase in PPAR-α activation potency and selectivity compared with the older fibrates.

However, statins also reduce remnant lipoproteins and small dense LDL particles,[80] which are components of the metabolic syndrome.[13] During the statin era, the additional atherosclerotic cardiovascular disease risk-reducing effects of fibrates in randomised controlled trials were, at best, modest. The clinical limitations of fibrates and PPAR-α agonists were shown by the negative results of the placebo-controlled randomised controlled trial with pemafibrate in patients with mild-to-moderate hypertriglyceridaemia and type 2 diabetes with low baseline HDL cholesterol and LDL cholesterol on a background of statin therapy.[81] Therefore, the use of fibrates and PPAR-α agonists should be restricted mainly for the treatment of severe hypertriglyceridaemia to prevent pancreatitis.[20]

Although fibrates might reduce cardiovascular events through very modest LDL cholesterol lowering,[79] in the statin era, fibrates are unlikely to add value in preventing atherosclerotic cardiovascular disease, although evidence of beneficial effects for patients with diabetic microangiopathy has been noted.[82] New drugs affecting triglyceride metabolism might also have a role in treating hyperchylomicronaemia and mitigating the risk of acute pancreatitis.

Another approach to reducing triglycerides is the use of fish oils—a combination of omega-3 fatty acids, eicosapentaenoic acid, and docosahexaenoic acid. In the pre-statin era, promising results were obtained in secondary prevention, but overall, their preventive value was inconsistent.[83] An explanation might be that, in omega-3 preparations, higher doses of eicosapentaenoic acid, but not docosahexaenoic acid, are selectively beneficial.[84] The favourable results of an open-label eicosapentaenoic acid trial[85] have been confirmed in a randomised controlled trial, in which synthetic icosapent ethyl—a purified ethyl ester of eicosapentaenoic acid—was compared with placebo in secondary prevention for patients with hypertriglyceridaemia treated with statins,[86]

	Mode of action	Notes
Agents targeting LDL cholesterol		
Orally administered antibodies of PCSK9 MK-0616 and NNC0385-0434	Inhibition of PCSK9	Successful in phase 2 randomised controlled trials; promotion of NNC0385-0434 has been discontinued due to portfolio competition;[92] for MK-0616, the CORALreef Outcomes (TIMI 77; NCT06008756) clinical outcome study is ongoing
Lomitapide (microsomal triglyceride transfer protein inhibitor)	Inhibition of the microsomal triglyceride transfer protein and induction of autophagic cell death via inhibition of mTOR	Already approved for homozygous familial hypercholesterolaemia (publication of the paediatric study results [NCT04681170] is awaited); might be potentially repurposed as an anti-cancer drug[93,94]
CRISPR-base-editing technique[95] with investigational drugs VERVE-101 and 102	Disruption of *PCSK9* expression in the liver	Study with Verve-101 was discontinued due to safety reasons; Verve-102 is using the same base editor and guide RNA but a different lipid nanoparticle than VERVE-101 for cell delivery system; VERVE-102 is being studied in an open-label, phase 1b, single ascending dose study (NCT06164730)
Obicetrapib (cholesteryl ester transfer protein inhibitor)	Inhibition of cholesterol ester transfer protein (due to increased catabolism) with statistically significant reduction of LDL cholesterol and apolipoprotein B concentrations	Phase 2 randomised controlled trials completed; phase 3 trials, including a large outcome trial (PREVAIL; NCT05202509) under way[96]
Exosome-based nanoplatform	LDL receptor mRNA delivery in familial hypercholesterolaemia	A new therapeutic approach for the treatment of homozygous familial hypercholesterolaemia; the first-in-human study is aimed to evaluate the safety and preliminary effectiveness (NCT05043181)
Agents targeting apolipoprotein C-III and angiopoietin-related protein 3		
Olezarsen (antisense oligonucleotide)	Inhibition of apolipoprotein C-III mRNA translation	Ongoing randomised controlled trials (eudraCT: 2021-002192-19 and 2021-003280-95)[25]
Evinacumab (fully human IgG1 monoclonal antibody)	Inhibition of ANGPTL3	Approved in 2021 by both the US Food and Drug Administration and the European Medicines Agency for the treatment of homozygous familial hypercholesterolaemia[97]
Zodasiran (siRNA)	Inhibition of *ANGPTL3* mRNA (thereby inhibiting hepatic synthesis)	Tested in a phase 2b randomised controlled trial of mixed hyperlipidaemia (NCT04832971; NCT04832971; NCT05217667; NCT03747224)[98]
Agents targeting severe hypertriglyceridaemia		
Plozasiran (siRNA)	Inhibition of *APOC3* mRNA	Tested in phase 1/2b randomised controlled trials (NCT05902598; NCT06347133; NCT06347003; NCT05413135; NCT05089084; NCT04720534; NCT04998201; NCT03783377)[99]
Olezarsen (siRNA)	Inhibition of hepatic synthesis of apolipoprotein C-III	Reduces triglycerides in familial chylomicronaemia (NCT06360237)[100]
Agents targeting lipoprotein(a)		
Pelacarsen (antisense oligonucleotide)	Inhibition of hepatic synthesis of apoprotein(a)	Lipoprotein(a) reduction >80%;[19] phase 3 randomised controlled trial ongoing (NCT04023552)
Muvalaplin (oral small molecule inhibitor)	Inhibition of lipoprotein(a) formation by blockage of the apolipoprotein(a)–apo B100 interaction	Lipoprotein(a) reduction 63–65% (NCT04472676);[19] further randomised controlled trials ongoing (NCT05778864; NCT05563246)
Olpasiran (siRNA)	Inhibition of hepatic synthesis of apolipoprotein(a)	Phase 3 randomised controlled trials ongoing (NCT05581303; NCT04270760; NCT04987320; NCT05481411)[19,101]
Zerlasiran (siRNA)	Inhibition of hepatic synthesis of apolipoprotein(a)	Well tolerated in phase 1/2 randomised controlled trials (NCT05537571; NCT04604402); caused strong reduction of plasma lipoprotein(a) concentrations with infrequent administration[19,101]
Lepodisiran (siRNA)	Inhibition of hepatic synthesis of apolipoprotein(a)	Phase 2 trials, phase 3 randomised controlled trial recruiting (NCT06292013)[19,101]
Agents targeting HDL cholesterol		
Obicetrapib (cholesteryl ester transfer protein inhibitor)	Inhibition of cholesterol ester transfer protein with statistically significant reduction of LDL cholesterol, apolipoprotein B, and lipoprotein(a) concentrations	Phase 2 randomised controlled trials completed, phase 3 trials underway, including a large outcome trial (PREVAIL; NCT05202509)[19,96,102]
CSL112 (human apolipoprotein A-I)	Promotion of reverse cholesterol transport	No reduction of atherosclerotic cardiovascular disease events in a randomised controlled trial[103]
Agents targeting other molecules		
Eprotirome and resmetirom (liver-directed, orally active thyroid hormone receptor-β agonists)	Likely reduction of hepatic secretion of VLDL and production of LDL, and increasing clearance of LDL cholesterol via the LDL receptor	These agents reduced LDL cholesterol, other atherogenic lipids, and lipoprotein concentrations in individuals in both the control group and homozygous familial hypercholesterolaemia group having standard therapy in randomised, placebo-controlled trials, but clinical use for dyslipidaemia is not promoted because of adverse effects; resmetirom improved liver fibrosis and was approved by the US Food and Drug Administration in 2024 for the treatment of metabolic dysfunction-associated steatotic liver disease[104,105]
Cholesin (gut-secreted hormone)	Inhibition of hepatic cholesterol synthesis	Secretion of cholesin is induced by cholesterol absorption; no clinical applications as of yet[106]
Gut microbiome manipulation	Conversion of cholesterol to coprostanol (which can be excreted in faeces) by microbial cholesterol dehydrogenases	No clinical applications as of yet[107]

(Table 2 continues on next page)

	Mode of action	Notes
(Continued from previous page)		
PCSK7 modulation	Some *PCSK7* variants are associated with hepatic fat accumulation, high plasma levels of triglycerides, low plasma levels of HDL cholesterol, and acute coronary syndrome	No clinical applications as of yet[108]

Apolipoprotein C-III is a potent inhibitor of lipoprotein lipase. *ANGPTL3* encodes a potent inhibitor of lipoprotein lipase and endothelial lipase. Details of siRNA-based drugs and corresponding clinical trials (with trial registration numbers) are listed elsewhere.[101] siRNA=small interfering RNA. CRISPR=Clustered Regularly Interspaced Short Palindromic Repeats.

Table 2: **Novel agents for dyslipidaemia targets in ongoing clinical trials**

and in an open-label randomised controlled trial in patients with coronary artery disease on statin treatment with a low eicosapentaenoic acid to arachidonic acid ratio.[87] On the basis of the positive results seen, icosapent ethyl was approved in 2021 for the secondary prevention of atherosclerotic cardiovascular disease in patients with moderately increased (>1·7 mmol/L) plasma triglyceride concentrations.[88] However, icosapent ethyl appears to exert its positive effects on advanced atherosclerotic cardiovascular disease, irrespective of triglyceride concentrations, via multiple pleiotropic effects. Icosapent ethyl also reduced cardiovascular events in patients with clinically relevant elevations of lipoprotein(a) concentrations.[89] Potential adverse effects related to induction of atrial fibrillation with icosapent ethyl should be considered.[88]

Directed at lipoprotein(a)

Lipoprotein(a) is composed of apolipoprotein(a) covalently linked to apoB-100.[19] The hepatic synthesis and plasma concentrations of lipoprotein(a) are mainly genetically determined. Lipoprotein(a) might reduce blood loss during parturition and accelerate wound healing, thereby having evolutionary advantages. Lipoprotein(a) is a unique carrier of oxidised phospholipids in the circulation, and oxidised phospholipid–apoB is a powerful driver of pro-inflammatory stimuli in the arterial wall.[90]

Despite increasing risk of atherosclerotic cardiovascular disease (specifically myocardial infarction) and calcific aortic stenosis, lipoprotein(a) has received much less attention than LDL cholesterol due to the unavailability of standardised and precise assays and the absence of suitable therapies to reduce lipoprotein(a) concentrations.[91] The resurgence of interest in lipoprotein(a) has been due to genetic studies that consistently suggest its causal role in atherosclerotic cardiovascular disease. On a per-particle basis, lipoprotein(a) appears to be more atherogenic than LDL.[19] Statins have little effect on lipoprotein(a), whereas PCSK9 inhibitors reduce lipoprotein(a) concentrations by 20–25%.[19] However, the independent benefit of lipoprotein(a) reduction by PCSK9 inhibitors is difficult to assess. This difficulty is because PCSK9 inhibitors effectively reduce LDL cholesterol, which in turn reduces atherosclerotic cardiovascular disease risk; therefore it is impossible to discern the potential role of simultaneous (and moderate) lipoprotein(a) reduction. Moreover, a substantial reduction in plasma lipoprotein(a) concentrations is probably needed for clinical effects to be noted.[91] Emerging siRNA-based pharmacotherapies yielding long-term inhibition of the hepatic synthesis of lipoprotein(a) are currently being studied in outcome trials and might lead to another change in therapeutic approach (table 2).[19]

Directed at HDL cholesterol

Hypoalphalipoproteinaemia, or low HDL cholesterol, was identified as an atherosclerotic cardiovascular disease risk marker in the 1950s, forgotten, and rediscovered in 1975.[109] HDL particles were considered important in so-called reverse cholesterol transport from the arterial wall back to the liver, and this concept led to an interest in identifying therapies to increase HDL cholesterol.

Nicotinic acid, a previously widely used medication to raise HDL cholesterol, is no longer indicated for clinical use (appendix pp 2,3). Great hopes were put on cholesterol ester transfer protein (CETP) inhibitors, which substantially increase HDL cholesterol.[110] However, the first CETP inhibitor paradoxically increased atherosclerotic cardiovascular disease events, and trials with other inhibitors were neutral, except for one trial testing anacetrapib, which showed that atherosclerotic cardiovascular disease events were modestly reduced, although the benefit was probably due to the simultaneous reduction in apoB-containing lipoproteins.[111] Randomised controlled trial results with the latest CETP inhibitor, obicetrapib (NCT04753606), are awaited to further clarify the potential relevance of CETP inhibition in preventing atherosclerotic cardiovascular disease.[96]

The plausible idea that improving the function of the HDL particles, not the concentration of HDL cholesterol, was beneficial aroused new interest in an old drug, probucol (appendix pp 3,4). The AEGIS II trial studied CSL112, the recombinant human apolipoprotein A-I, the major apoprotein in HDL, complexed with phospholipids, which mimicked the natural, nascent pre-β HDL particle, and was therefore considered to potentially promote cholesterol efflux in patients with acute atherosclerotic cardiovascular disease.[103] However, study results were negative.

In summary, HDL cholesterol is currently considered a risk marker and a component of a standard lipid profile essential to estimate LDL cholesterol, but not a therapeutic target.[20] However, the absence of causality between HDL cholesterol and atherosclerotic cardiovascular disease has been challenged in some mendelian randomisation studies.[112,113]

Present barriers to treatment success of statins

Statins are very safe and well tolerated, even in frail individuals.[32,114,115] Musculoskeletal complaints truly related to statin use are rare, and serious adverse effects, such as rhabdomyolysis or immune-mediated necrotising myopathy, are very rare.[115] Statin treatment might hasten diabetes onset in a minority of individuals at risk.[46] The mechanisms whereby statins can accelerate diabetes onset are still undefined and multifactorial, and their clinical significance is probably minor. Patients with diabetes also benefit from statin treatment.[44] Although known to affect liver enzymes, statins are not hepatotoxic, with potential benefit in metabolic dysfunction-associated steatotic liver disease.[48]

The main challenges for preventive therapies, the benefits of which are not immediately visible, are starting too late, suboptimal treatment, and poor adherence. The diagnosis of dyslipidaemias overall needs to improve, but even more so for the severe forms, such as familial hypercholesterolaemia; educational campaigns by pathology national registers and flagging of atypical values of laboratory tests might contribute to this goal. Statin treatment has suffered from the drucebo and nocebo effects, bad publicity, and the spread of misinformation or disinformation in social media,[116,117] leading to unnecessary discontinuation of treatment and increased atherosclerotic cardiovascular disease risk. However, therapeutic and clinical inertia that delay commencement of appropriate treatment are also to blame. For example, achievement of the currently recommended 2019 European Society of Cardiology and European Atherosclerosis Society-guided LDL cholesterol goals (panel 1) in primary and secondary prevention is suboptimal worldwide, despite straightforward and inexpensive treatment options. In HICs, treatment gaps were observed in the EUROASPIRE surveys[118] and the recent multinational European SANTORINI study.[119] The latter showed that 80% of patients at high risk and very high risk did not achieve the current target of LDL cholesterol of less than 1·4 mmol/L (55 mg/dL). The underlying factors include underestimation of the atherosclerotic cardiovascular disease risk, scepticism, nocebo effects, and underutilisation of combination therapies. Another important factor might be fear of diabetes related to statin use. The modest glucometabolic harm is unlikely to exceed the atherosclerotic cardiovascular disease benefits of statins,[120] and it can be mitigated by a healthy diet, physical activity, and weight control. Barriers and solutions to treatment access and adherence (panel 2[122,123]) must be considered at the patient, provider, health-care system, and societal and economic levels. These factors are amplified in their importance in under-resourced communities, even in HICs.

The challenges are worse in LMICs, where suboptimal health care and diagnostic procedures, digital illiteracy, and lower availability and affordability of lipid-lowering drugs are further contributory factors.[124] For example, in a diverse sample of LMICs, statins were used only by one in ten eligible individuals for primary prevention of atherosclerotic cardiovascular disease and by one in five of the eligible individuals for secondary prevention of the disease.[125] Very low use of statins in the secondary and high-risk primary prevention population with other cardiovascular risk factors was observed in primary care in Brazil.[126,127] There are, however, substantial regional and country-level differences.

With atherosclerotic cardiovascular disease emerging as an increasing health-care burden in LMICs, increasing the use of low-cost statins and ezetimibe therapies is urgently needed to achieve WHO targets (statins are included in the WHO Model List of Essential Medicines). Studies are especially needed to investigate the best ways to facilitate implementation into primary health care. Although generic statins are hardly an economic issue in HICs, cost concerns can hinder the use of new drugs even in high-income settings.

For more on the **WHO Model List of Essential Medicines** see https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02

Therapeutic challenges also include when to avoid therapy (eg, with a zero coronary calcium score) or when to deprescribe. Individuals not likely to benefit from therapy should be recognised, and statins are less likely to be beneficial in end-stage organ diseases, such as advanced chronic kidney disease or non-ischaemic heart failure, dementia, or end-of-life care.[9,32,128] Even if not affecting the basal condition, statins can prevent atherosclerotic cardiovascular disease-dependent complications. Therefore, deprescribing a statin should follow consideration of all relevant individual factors, particularly expected lifetime.[129]

Prevailing questions and future directions

Three decades of statin use since the 4S have yielded many lessons. The notion that plasma LDL cholesterol is pivotal to the development of atherosclerotic cardiovascular disease has been strengthened.[3,8] The concept of cumulative exposure to, or the burden of, LDL cholesterol is underscored by genetic evidence and is fundamental for the design of preventive strategies.[8,130] This concept emphasises primordial prevention—ie, focus on the young to prevent atherosclerotic risk factors—to ensure that dyslipidaemia and other conditions do not develop in the first place and to recognise genetic conditions, such as familial hypercholesterolaemia or high lipoprotein(a), as early as possible.[131] Further challenges include resisting misinformation about treatment, improving accessibility and adherence to LDL cholesterol reduction (panel 2), and better managing the residual risk of atherosclerotic

***Panel* 2: How to improve adherence to and accessibility of dyslipidaemia therapy at various levels**

Patient and societal level

- Promote educational initiatives about the benefits and harms of treatment
- Address social and economic determinants of barriers to therapy

Provider level

- Plan treatments with the patient
  - Listen to patients' wishes and needs
  - Find out about potential prejudices and false attitudes (eg, caused by social media)
- Find out hindrances and seek solutions
  - Ask the patient about barriers and potential fears of medication
  - Consider pill burden, cognition, life situation, the need for assistance (ie, advice according to level of education), and economical aspects
- Discuss and clearly define the goals of treatment and its expected benefits
- Discuss the potential adverse effects of the treatment in question
  - Advise on how to act if side-effects occur
  - Place potential side-effects into context regarding benefits
- Find out attitudes and fears related to treatment
  - Inform and provide facts about the treatment, with respect to patients' attitudes
- Choose the simplest way possible for adequate treatment
  - Form of dosing, possible combination therapy (eg, polypill)
  - Ascertain the right technique (eg, for injections)
- Remember multidisciplinary support
  - Consider nurses and pharmacists, who are often in close contact and trusted by patients; it is also important that their advice is in line with advice by the physician
- Engage family members and other support chains
- Avoid blaming the patient for non-adherence; instead, try to find solutions together
- Assess adherence at each visit and recognise potential problems
  - Document the medication plan
  - Ascertain adequate follow-up measures
  - Encourage the patient to contact a health-care professional for potential questions about treatment
  - Encourage the patient to share problems during treatment (eg, asking whether the patient has been able to take their medication) or about potential suspicions concerning treatment
- Assess chemical indicators of adherence
  - Consider digital possibilities (eg, drugs with ingestible sensors, patient apps, a physician portal, and reminders sent to mobile phones that require a reply)

Health-care system level

- Implement contextual and country-specific guidelines, such as the international guidelines from the European Society of Cardiology and European Atherosclerosis Society,[20] Japan Atherosclerosis Society,[21] American Heart Association and American College of Cardiology,[22] and World Heart Federation,[121] or national guidelines
- Promote educational initiatives and tools for patients and providers (given that the pharmaceutical industry seldom provides these aspects for generic drugs)
- Explain alternatives to treatment and treatment policy: for example, multidisciplinary teams often work better than a physician alone to secure long-term preventive success; transitions between hospital and community-based care should be seamless
- Consider whether non-prescription (over-the-counter) statins might improve access to medication
- Assess technology that can be useful to assist selection and follow-up[122]

Modified from Karalis (2023).[123]

cardiovascular disease through the control of other atherogenic lipoproteins (table 2).[19,25,92–100,102–108] New treatments require precise data on mechanisms and safety, and insights provided by loss-of-function gene variants have helped to understand these challenges better.

Besides protein inhibition or antagonism, the new therapeutic techniques include inhibition of translation at the messenger RNA level (ie, antisense oligonucleotides or siRNA) and introduction of loss-of-function variants through base editing.[101,132] Because these techniques have powerful lipid-lowering properties and might have permanent action, they could revolutionise dyslipidaemia treatment by improving adherence and reducing the high residual risk of atherosclerotic cardiovascular disease. However, potential safety issues must be clarified.[133]

In developing PCSK9 inhibitor-based therapy, the efficacy and safety of oral forms (eg, MK-0616 and NN0385-0434) have also been reported in phase 2 trials,[92] and MK-0616 is currently being tested in a clinical outcome study (NCT06008756). Because PCSK9 degrades the LDLR, it is an attractive target for novel therapeutics, such as genetic or epigenetic editing methods.[133,134] For example, the use of the CRISPR-Cas9 gene editing system can provide an accurate and efficient means to generate sequence-specific changes in the genome.[95,135] A one-base pair shift in the *PCSK9* gene results in production of non-functional PCSK9 protein, leading to potentially lifelong reductions in plasma LDL cholesterol concentrations. Gene editing of other proteins that control lipid and lipoprotein metabolism is likely to follow. Phase 1 clinical studies in heterozygous familial hypercholesterolaemia have started to define the efficacy and safety of base editing of *PCSK9*. The Heart-2 phase 1b clinical trial (NCT06164730) involves VERVE-102, a liver single-course base-editing medicine that aims to inactivate PCSK9. However, there are early clinical concerns of safety, and considering the permanent effects of these therapies, ruling out off-target effects (eg, mutations in healthy genes or chromosomal damage) is essential. Furthermore, permanent suppression might result in adverse events, such as impaired resistance to infection.[133] As a result, regulatory agencies require substantially longer observation periods than what has been done so far to acquire safety data.

Silencing *PCSK9* and preventing irreversible change to DNA and at least some of the potential associated risks could be achieved in another way—namely, by epigenome editing, which can be used to affect gene expression without changing the genome sequence.[136] In preclinical studies, epigenetic editors were transiently delivered in vivo and their effects on PCSK9 and LDL cholesterol concentrations were long lasting.[136]

Loss-of-function variants affecting proteins and enzymatic pathways, important in triglyceride metabolism, have opened new possibilities for other dyslipidaemia drug targets.[137] Chylomicrons and VLDL

undergo intravascular lipolysis by lipoprotein lipase and are converted to potentially atherogenic remnant particles. Apolipoprotein C-III and angiopoietin-related protein 3 (ANGPTL3) and 4 (ANGPTL4) are potent inhibitors of lipoprotein lipase. Loss-of-function variants in their genes are associated with increased lipoprotein lipase activity, reduced triglycerides, and reduced risk of atherosclerotic cardiovascular disease.[138,139] However, only individuals who are homozygous for loss-of-function variants in *ANGPTL3* with at least 50% reduction in activity have very low LDL cholesterol concentrations, whereas individuals who are heterozygous have little or no LDL cholesterol reduction. These discoveries enabled the development of apolipoprotein C-III and ANGPTL3 inhibitors (table 2). These drugs might be useful, especially in mixed hyperlipidaemia, in addition to statins and in severe hypertriglyceridaemia, to prevent acute pancreatitis. Outcome trials are ongoing and will give more information about efficacy and safety of these novel therapies (NCT05355402; NCT05079919; NCT05089084; NCT06347133; NCT03452228; NCT05611528).[140]

Homozygous familial hypercholesterolaemia is a rare genetic disorder due to variants in *LDLR, APOB, PCSK9,* or rarely *LDLRAP1,* leading to very high plasma LDL cholesterol and resistance to medications, which act mainly by upregulating LDLR activity. Lipoprotein apheresis and liver transplant have been the main therapeutic options, but more efficient drug treatments that act independently of LDLR function have been developed. Evinacumab and lomitapide, inhibitors of ANGPTL3 and the microsomal triglyceride transfer protein respectively, are already approved for homozygous familial hypercholesterolaemia.[141] Trials with zodasiran, a siRNA targeting *ANGPTL3*, are also underway (NCT04832971; NCT04832971; NCT05217667; NCT03747224).[98,101]

Several drugs that interfere with apolipoprotein(a) synthesis have been recently tested in clinical trials (table 2).[19] If such studies yield positive results, they should provide definitive evidence of a causal role of lipoprotein(a) in atherosclerotic cardiovascular disease.

Potential novel agents for the treatment of dyslipidaemias include liver-directed thyroid receptor β (TRβ)-selective thyroid analogues (eg, eprotirome, resmethrin) without cardiac effects, which lowered LDL cholesterol, triglycerides, and also lipoprotein(a) in both control individuals and individuals with familial hypercholesterolaemia.[104] Due to subsequent safety concerns, liver-directed TRβ-selective thyroid analogues have not been promoted for dyslipidaemia. However, these drugs can benefit patients with metabolic dysfunction-associated steatotic liver disease by correcting the dysfunctional TR-β signalling and fibrosis[105] and, in 2024, resmetirom was approved by the US Food and Drug Administration to treat this condition. Recently discovered cholesin, a gut-derived hormone, inhibits hepatic cholesterol synthesis and VLDL secretion, reducing plasma cholesterol concentrations.[106] Manipulation of the gut microbiome might also provide a new approach to control cholesterol metabolism.[107,142] The development of specific adipose triglyceride lipase activators could potentially lead to a novel approach to reverse endothelial dysfunction and prevent atherosclerotic cardiovascular disease in patients with dyslipidaemia and metabolic syndrome.[76]

Conclusion

Since the revolutionary results of the 4S were published in 1994, the landscape of opportunity for dyslipidaemia therapy has undergone further drastic change. Both diagnostic and therapeutic strategies for various dyslipidaemias are in a very dynamic phase,[143,144] with new targets and treatment opportunities bringing possibilities for population health improvement beyond what is attainable with statins.[136] Novel therapeutic techniques offer a seemingly ideal way to abolish most atherosclerotic cardiovascular disease by knocking out harmful proteins using vaccination-type treatment or genetic manipulation early in life. However, the use of gene editing approaches necessitates demonstration of valid data concerning safety and cost-effectiveness, which might require long follow-up periods to prove.[133] Consequently, generic statin therapy, ideally combined with ezetimibe and started early, should remain a general and cost-effective plan to combat atherosclerotic cardiovascular disease worldwide for years to come.[29,131,145,146] Various aspects of the future roadmap to promote global dyslipidaemia therapy are listed in panel 3.[121] In secondary prevention, residual risk is a central problem, and in addition to effective treatment of all pro-atherogenic lipids, control of inflammation, treating comorbid diabetes with modern drugs, inhibiting thrombosis, and treating other atherosclerotic

***Panel* 3: Global roadmap for better dyslipidaemia therapy**

- Emphasise the importance of the life course (ie, primordial prevention)
- Focus on lifetime risk
- Promote affordable testing
- Implement universal and early screening for genetic dyslipidaemias
- Ensure availability of affordable, effective, and cost-effective treatment regimens
- Improve health literacy to combat misinformation
- Promote multidisciplinary teams and applications to support adherence and patient-centred therapy
- Improve use of pragmatic trials and trials with high-quality imaging to reduce costs
- Ensure equity in trials by collecting and reporting sex-disaggregated data, data from multiple ethnic groups, and data from patients with multimorbidity and frailty

Modified from Ray et al (2022).[121]

cardiovascular disease risk factors are required.[37,78,147] Especially in LMICs, a population strategy with an inexpensive polypill-type therapy[148,149] might be an affordable umbrella treatment to relieve morbidity and mortality, reduce the burden of health care, and decrease costs due to cardiovascular diseases—which remain, to this day, the leading cause of mortality worldwide.

Contributors

All authors contributed to the literature search, data collection and interpretation, manuscript writing, and visualisation (ie, tables and panels). TES wrote the first draft of the manuscript. All authors verified and approved the final version of the manuscript. In memoriam of Prof Akira Endo (1933–2024), the Japanese biochemist who discovered mevastatin, which led to the development of all statins used today.

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