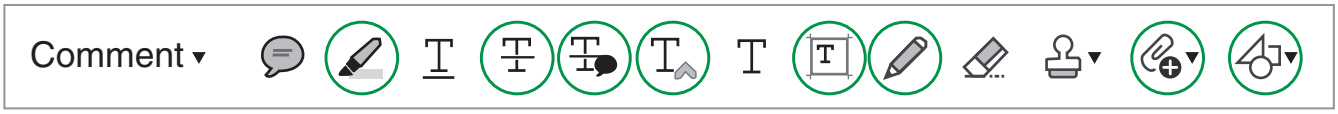
Page Proof Instructions and Queries

Journal Title: European Journal of Preventive Cardiology (CPR)

Article Number: 845314

Thank you for choosing to publish with us. This is your final opportunity to ensure your article will be accurate at publication. Please review your proof carefully and respond to the queries using the circled tools in the image below, which are available **by clicking "Comment"** from the right-side menu in Adobe Reader DC.*

Please use *only* the tools circled in the image, as edits via other tools/methods can be lost during file conversion. For comments, questions, or formatting requests, please use T. Please do *not* use comment bubbles/sticky notes.



*If you do not see these tools, please ensure you have opened this file with Adobe Reader DC, available for free at get.adobe.com/reader or by going to Help > Check for Updates within other versions of Reader. For more detailed instructions, please see us.sagepub.com/ReaderXProofs.

No.	Query
	Please confirm that all author information, including names, affiliations, sequence, and contact details, is correct.
	Please review the entire document for typographical errors, mathematical errors, and any other necessary corrections; check headings, tables, and figures.
	Please confirm that the Funding and Conflict of Interest statements are accurate.
	Please ensure that you have obtained and enclosed all necessary permissions for the reproduction of artistic works, (e.g. illustrations, photographs, charts, maps, other visual material, etc.) not owned by yourself. Please refer to your publishing agreement for further information.
	Please note that this proof represents your final opportunity to review your article prior to publication, so please do send all of your changes now.
AQ: 1	Author affiliation 6: please add the city and country.
AQ: 2	Author affiliation 9: please add the city.
AQ: 3	please provide a list of keywords.
AQ: 4	'MACE' has been defined in the text as 'major adverse cardiac event' and in the Figures and Tables as 'major adverse cardiovascular event.' Please check.
AQ: 5	please check that 'by 17%' and 'by 25%' are correct in the sentence 'A recent meta-analysis including 54 trials with 97,910 patients showed that PCSK9 inhibitors significantly reduced the risk of major adverse cardiac events (MACEs) by 16%, non-fatal myocardial infarction (MI) by 17% and stroke by 25%.'.
AQ: 6	in the subsection 'High-dose eicosapentaenoic acid' please check that the percentages are presented correctly in ' Lowering of triglyceride was −26% to −31% and of non-HDL-C −7.5% to −9.6% versus baseline'.
AQ: 7	in the paragraph beginning 'The efficacy and safety of icosapent ethyl', please check that '–32.9%' is correct in 'Restricting analysis to patients with triglyceride ≥750 mg/dL, the drop was more significant, that is, −45.4% and −32.9%,'.
AQ: 8	in the paragraph beginning 'The efficacy and safety of icosapent ethyl', please check that '–7%' is correct in 'and total HDL (–7%),'.
AQ: 9	please check that 'oxidized-LDL' is correct in the paragraph beginning 'The efficacy and safety of icosapent ethyl'.
AQ: 10	Refs. 4 and 5: please check that the amended publication details are correct.
AQ: 11	Ref. 8: please check that the amended publication details are correct.
AQ: 12	Ref. 19: please check that the amended publication details are correct.

AQ: 13	Ref. 41: please check the author name and add the publication details.
AQ: 14	Ref. 42: please add the year of origination of the material before the accessed date. Please add the date that you last accessed the website.
AQ: 15	Ref. 43: please add the date that you last accessed the website.
AQ: 16	Ref. 44: please add the volume number.
AQ: 17	please note that references after 57 have been renumbered to allow 146 to be cited in sequence in Table 1.
AQ: 18	Ref. 58: please add the volume and page/article number.
AQ: 19	Ref. 66: please check that the amended publication details are correct.
AQ: 20	ref. 67: please complete the author names. Please add the volume and page numbers or Epub date.
AQ: 21	Ref. 68: please add publication/access details if applicable.
AQ: 22	Ref. 71: please check that the amended publication details are correct.
AQ: 23	Ref. 80: please check that the amended publication details are correct.
AQ: 24	Ref. 100: please add the date that you last accessed the website.
AQ: 25	Refs 101 and 102: please add the page/article number.
AQ: 26	Ref 106: please add the page/article number.
AQ: 27	Ref 109: please check that the amended publication details are correct.
AQ: 28	Ref. 112: please complete the publication/access details.
AQ: 29	Ref 139: please check that the amended publication details are correct.
AQ: 30	Refs 141 and 142: please add publication/access details.
AQ: 31	Ref 145: please check that the amended publication details are correct.
AQ: 32	Figure 1: Symbols after SR-BI, Cholesterol efflux, etc. have not reproduced. Please indicated what these should be or that they should be deleted.
AQ: 33	Figure 1: please define LDLR, LPL, PPRE and RXR in the legend.
AQ: 34	Table 1: please check that minus signs are what was intended in the LDL-C lowering column.

European Journal of Preventive Cardiology

ESC European Society of Cardiology

Review

European Journal of Preventive Cardiology
0(00) 1–21

DOI: 10.1177/2047487319845314
journals.sagepub.com/home/ejpc

SAGE

Recent advances in synthetic pharmacotherapies for dyslipidaemias

Cesare R Sirtori[1], Shizuya Yamashita[2,3,4], Maria Francesca Greco[5], Alberto Corsini[5,6], Gerald F Watts[7,8,9] and Massimiliano Ruscica[5]

Abstract

Despite the demonstrated benefits of statins and injectable biologics, there is a need for new and safe oral agents for addressing classical lipid targets, low-density lipoprotein cholesterol (LDL-C), triglycerides and high-density lipoprotein cholesterol (HDL-C). LDL-C is unquestionably causal in the development of atherogenesis and atherosclerotic cardiovascular disease, but new options are required to address triglyceride-rich lipoproteins and lipoprotein(a). For hypercholesterolaemia, pitavastatin provides a very low dose and potent statin that does not adversely affect glucose metabolism; bempedoic acid acts at a biochemical step preceding hydroxymethylglutaryl-CoA reductase and is not associated with muscular side effects. For hypertriglyceridaemia, pemafibrate displays a unique and selective agonist activity on peroxisomal proliferator activated receptor-α that does not elevate homocysteine or creatinine. Although omega-3 fatty acids supplementation is not effective in secondary prevention, high dose eicosapentaenoic ethyl ester can lead to a remarkable fall in first and recurrent events in high risk patients with hypertriglyceridaemia/low HDL-C. Gemcabene, a dicarboxylic acid regulating apolipoprotein B-100 is effective in reducing both cholesterol and triglycerides. Among cholesteryl ester transfer protein antagonists that elevate HDL-C, only anacetrapib reduces cardiovascular events. Probucol stimulates reverse cholesteryl ester transport, lowers LDL-C stabilizing plaques and may lower incidence of cardiovascular events. These agents, which act through novel mechanisms, afford good and potentially safe treatment choices that may increase adherence and the attainment of therapeutic targets.

Keywords
[AQ3]

Received 24 January 2019; accepted 1 April 2019

Introduction

The availability of synthetic lipid lowering drugs for cardiovascular prevention is comparatively narrow. As of now, there are a little more than 10 synthetic agents for use, in addition to the newer biosynthetic agents, for example, monoclonal antibodies[1] or antisense oligonucleotides.[2] There is also a need for novel agents that are more tolerable than statins with low risk of myalgia and new-onset of diabetes.

The present review will investigate synthetic orally administered pharmacotherapies, in advanced development or currently in use. These agents target plasma cholesterol (pitavastatin and bempedoic acid), triglyceride (high dose eicosapentaenoic acid ethyl ester and pemafibrate), both cholesterol and triglyceride (gemcabene), and the regulation of high-density lipoprotein

[1]Centro Dislipidemie, A.S.S.T. Grande Ospedale Metropolitano Niguarda, Milan, Italy
[2]Rinku General Medical Centre, Izumisano, Japan
[3]Department of Community Medicine, Osaka University Graduate School of Medicine, Suita, Japan
[4]Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan
[5]Department of Pharmacological and Bimolecular Sciences, Università degli Studi di Milano, Milan, Italy
[6]Multimedica, IRCCS, [AQ1]
[7]School of Medicine, Faculty of Health and Medical Sciences, University of Western Australia, Perth, Australia
[8]Lipid Disorders Clinic, Cardiometabolic Services, Department of Cardiology, Royal Perth Hospital, Australia
[9]Familial Hypercholesterolaemia Australia Network, Australia [AQ2]

Corresponding author:
Massimiliano Ruscica, Università degli Studi di Milano, Via Balzaretti 9, 20133 - Milan, Italy.
Email: massimiliano.ruscica@unimi.it

(HDL; cholesteryl ester transfer protein (CETP) inhibitors and probucol analogues). For this purpose, by using Pubmed.gov, we revised available English-language studies published from January 1998 to March 2019 and relevant to the key clinical questions discussed in this review. Search terms included pitavastatin, bempedoic acid, ETC-1002, pemafibrate, K-877, omega-3 fatty acids, icosapent ethyl, gemcabene, CETP inhibitors and probucol.

Low-density lipoproteins (LDLs) are unquestionably causal for the development of atherosclerotic cardiovascular disease (ASCVD). Recently, Silverman et al. have evaluated the association between lowering of LDL cholesterol (LDL-C) and cardiovascular risk reduction across different statin and non-statin trials.[3] The relative risk reduction in major cardiovascular events was similar for all drug classes (statins, bile acid sequestrants, ezetimibe and fibrates), and the lower achieved LDL-C levels (not percentage reductions) were associated with a reduced incidence of events.

Although not within the remit of the present review, it is noteworthy to mention that a major therapeutic boost in the field of lipidology has come from the approval of two fully human monoclonal antibodies, that is, alirocumab (IgG1) and evolocumab (IgG2), against the proprotein convertase subtilisin/kexin type 9 (PCSK9), a key-player in the regulation of LDL-C. These agents can reduce LDL-C by approximately 45–60% when used alone or in combination with a statin.[4] A recent meta-analysis including 54 trials with 97,910 patients showed that PCSK9 inhibitors significantly reduced the risk of major adverse cardiac events (MACEs) by 16%, non-fatal myocardial infarction (MI) by 17% and stroke by 25%. No differences between groups (PCSK9 inhibitors versus controls) were found for all-cause mortality, cardiovascular deaths, heart failure or unstable angina.[5] Interestingly, PCSK9 inhibitors and statins show similar effects on cardiovascular risk reduction per mg/dL reduction in LDL-C when the same duration of therapy is considered, that is, −14% (0–1 year of treatment), −17% (1–2 years of treatment) and −20% (2–3 years of treatment).[6] [AQ4] [AQ5]

Beyond LDL-cholesterol alone and familial hypercholesterolaemia, ASCVD risk is also dependent on a cluster of metabolic abnormalities, from familial combined hyperlipidaemia (most with elevated LDL-C and triglyceride),[7] familial hypertriglyceridaemia (elevated very-low density lipoprotein (VLDL) levels),[7] metabolic syndrome and related condition, such as type 2 diabetes (T2D), referred to as the atherogenic lipid phenotype, which is characterized by elevated fasting and post-prandial levels of triglyceride-rich lipoproteins and their remnants, low levels of HDLs, accumulation of small dense LDL with elevated apolipoprotein B (apoB) concentrations.[8]

Although the magnitude of contribution of triglyceride to cardiovascular risk is evident both from long-term prospective studies[9] and a recent Mendelian randomization analysis,[10] the mechanisms by which triglyceride-rich lipoproteins are atherogenic are still unclear.[11] Triglyceride-rich lipoproteins may penetrate the arterial wall and, due to the interaction between positively charged residues on apoB and negatively charged groups on the arterial wall proteoglycans, these lipoproteins are retained within the sub-endothelial space and after oxidative modification lead to the development of atherosclerotic plaques and ASCVD.[12] Moreover, the lipolysis of triglyceride-rich lipoproteins rich in cholesterol and apolipoprotein E (apoE) releases toxic products, for example, oxidized free-fatty acids and lysolecithin, inducing further endothelial cell inflammation and coagulation.[13]

Epidemiological and clinical studies link low levels of HDL with an increased risk of cardiovascular disease, although a direct causal role for HDL remains controversial.[14] Therapeutic interventions aimed at increasing HDL levels and reducing residual ASCVD risk in optimally drug treated patients have not hitherto provided convincing results. Among these therapeutic strategies, the inhibition of CETP has provided dose-dependent HDL-C elevations of 100% or more.[15] CETP inhibitors have not offered sufficient evidence to underpin their clinical use,[16] but the newer CETP antagonist TA-8995 merits consideration.[17] Probucol provides a unique example of an agent that selectively stimulates reverse cholesteryl ester transport and also deserves review. These therapeutic agents offer an innovative strategy for managing patients with severe and less severe dyslipidaemias (Figure 1).

LDL lowering

Pitavastatin

There is strong evidence that LDL-C lowering with statins reduces the risk of ASCVD in primary and secondary prevention, regardless of sex, age and diabetes.[18,19] By inhibiting the biosynthesis of cell cholesterol, statins result in an increased expression of LDL-receptors and increased uptake of LDL-C from the circulation. A meta-analysis on trials of statin therapy demonstrated a 22% reduction of major events over five years, that is, coronary death, non-fatal MI, coronary revascularization or stroke, for each 38.7 mg/dL (1 mmol/L) fall in LDL-C.[20] There is also evidence that higher doses of the same statin result in a further reduction in the risk of a cardiovascular disease (CVD) event.[21] Indeed, among trial participants treated with

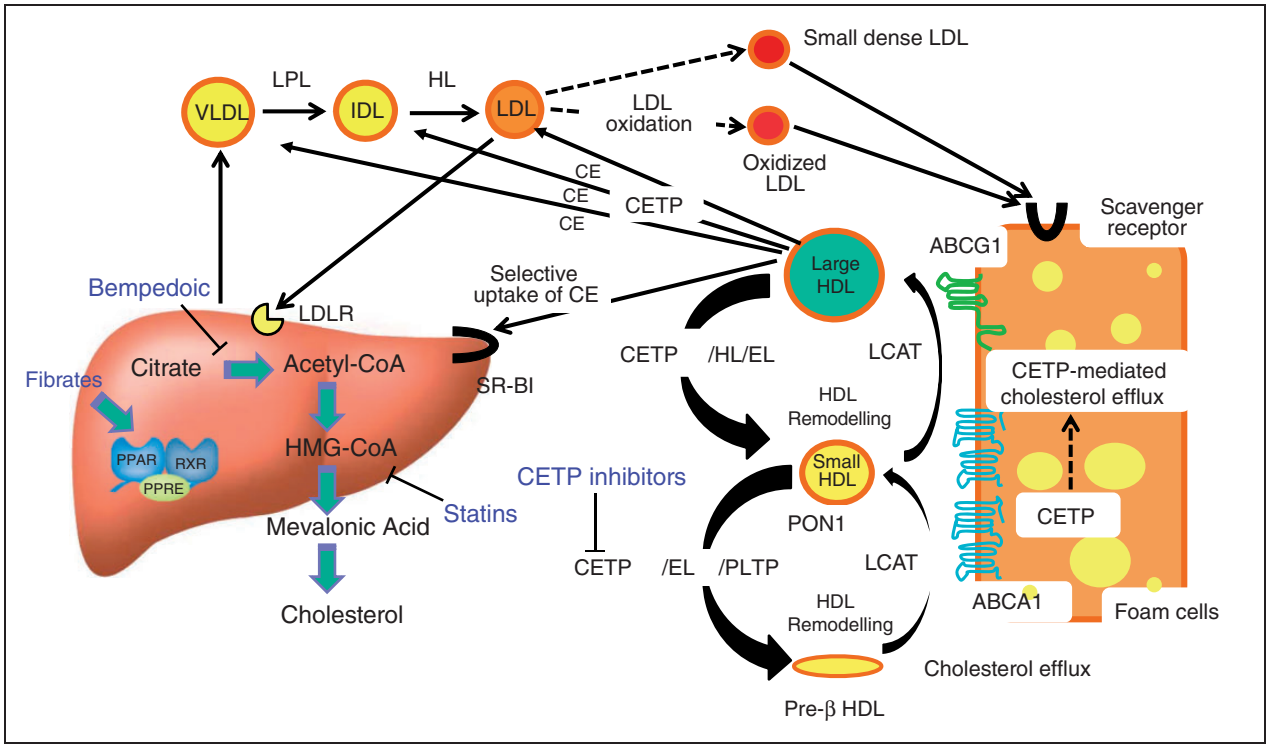


Figure 1. Mechanisms of action of the proposed synthetic drugs. *Statins* act by decreasing cell cholesterol by selectively inhibiting the enzyme HMG-CoA reductase; *ETC-1002* reduces the production of cytosolic acetyl-coenzyme A, precursor of the mevalonate pathway of cholesterol biosynthesis; *fibrates* non-selectively bind two or more PPARs; CETP inhibitors decrease CE and triglyceride exchange between lipoproteins; the probucol anti-atherogenic activity is attributable to different mechanisms. The stimulated cholesterol efflux is associated with an enhanced reverse cholesterol transport, consequent to the activation of CETP and raised scavenger receptor class B type I. The apparent reduction of HDL cholesterol by probucol may be due to remodelling by an endothelial lipase-mediated pathway: remodelled HDL has an increased preβ1-HDL content, responsible for a raised cell lipid efflux. These mechanisms can be responsible for the anti-atherogenic effects of probucol, in spite of the inhibitory activity on ABCA1-mediated cholesterol efflux. The reduction of LDL cholesterol by probucol may be consequent to an enhanced LDL catabolism, independent of the LDL receptor. The raised PON1 activity of HDL may protect LDL from peroxidation.
ABCA1: ATP-binding cassette transporter A1; ABCG1: ATP-binding cassette transporter G1; CE: cholesteryl ester; CETP: cholesteryl ester transfer protein; EL: endothelial lipase; HL: hepatic lipase; IDL: intermediate density lipoprotein; HDL: high-density lipoprotein; LCAT: lecithin:cholesterol acyltransferase; LDL: low-density lipoprotein; LDLR; ▮▮; LPL: ▮▮; PLPT: phospholipid transfer protein; PON1: paraoxonase 1; PPAR: peroxisomal proliferator activated receptor; PPRE: ▮▮; RXR: ▮▮; SR-BI: scavenger receptor class B type I; VLDL: very low-density lipoprotein [AQ32] [AQ33]

high-dose statin therapy, patients reaching very low LDL-C levels have a lower risk of major cardiovascular events than those achieving moderately low levels of LDL-C.[22] However, the clinical benefit of using a high compared with a low dose statin observed in Caucasians remains unclear in Asians and African populations. Recently, the REAL-CAD (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease) secondary prevention trial in Asians showed that high-dose pitavastatin (4 mg/day) can significantly reduce cardiovascular events compared with a lower dose of the agent (pitavastatin 1 mg/day).[23]

Compared with the other statins, pitavastatin contains a unique cyclopropyl group allowing avid interaction with the binding-site residues of HMG-CoA reductase that protects the drug from metabolism by the cytochrome P450 (CYP) enzymes. Pitavastatin is modestly metabolized by CYP2C9 and CYP2C8 but not by CYP3A4, being mainly excreted via biliary secretion and subject to entero-hepatic circulation. By this mechanism, pitavastatin has a reduced potential for drug–drug interactions.[24] This statin exhibits good bioavailability (60%), being rapidly absorbed after oral administration and reaching peak plasma concentrations within 1 h; it is highly bound to proteins in human plasma, mainly to albumin, with a mean volume of distribution of approximately 148 L.[25]

The efficacy and safety of pitavastatin have been confirmed in a wide range of individuals (e.g. elderly[26] and adolescents with familial hypercholesterolaemia,[27] patients with a wide range of metabolic or

auto-immune disease[28] or HIV[29]); no apparent diabetogenic effects were acknowledged.[30,31] In the most recent data from the REAL-CAD trial, 13,054 patients with stable coronary artery disease were randomized to either pitavastatin 1 mg or pitavastatin 4 mg daily (Figure 2). LDL-C was reduced by a further 16% in the high-dose group and although serum high-sensitivity C-reactive protein (hs-CRP) levels were low at baseline in both groups, pitavastatin 4 mg reduced these levels up to 0.49 mg/dL. The effect on clinical outcomes was more robust in patients given 4 mg *vs.* 1 mg, with a 19% reduction in the primary endpoint, that is, the cumulative four-year incidence of a composite of cardiovascular death, non-fatal MI, non-fatal ischaemic stroke, or unstable angina requiring emergency hospitalization (Table 1). The absolute risk reduction was 1.1%, with a number-needed-to-treat (NNT) of 63 over five years. For the secondary key-endpoints, the absolute risk reduction was 1.9% in favour of pitavastatin 4 mg, with a NNT of 41 over five years. All-cause mortality was reduced by 19%, MI by 43% and need for revascularization by 14%. Risk reduction was consistent across sex, diabetes mellitus, baseline levels of LDL-C, triglyceride and body mass index. Adverse effects, including myalgia and rhabdomyolysis, were low with no between-group differences.[32]

Finally, in a head-to-head comparison between pitavastatin, atorvastatin and rosuvastatin in post-MI patients, pitavastatin was associated with the lowest cumulative incidence of new-onset diabetes (NOD), that is, 3% *vs.* 8.4% atorvastatin and 10.4% (rosuvastatin), $p = 0.001$ for both. In multivariate analysis, atorvastatin versus pitavastatin resulted in a hazard ratio of 2.54 (95% confidence interval (CI): 1.1–5.7; $p = 0.02$) and rosuvastatin versus pitavastatin in a hazard ratio of 3.68 (95% CI: 1.6–8.3; $p = 0.0008$).[33] Indeed, while treatment with statins reduces the risk of ASCVD event, including those with T2D, statin treatment also increases the likelihood of NOD in patients with risk factors for diabetes, for example, familial history of diabetes, female gender, older age (especially with higher doses of statins), of Asian origin and longer duration of use.[34]

Brief summary. Pitavastatin raises HDL phospholipids, improves HDL-mediated efflux capacity and HDL antioxidant properties. Although the established cardiovascular benefits of statin therapy far outweigh the risk of adverse effects, NOD with statins may be reduced by the use of pitavastatin. This agent has neutral effects on glycaemic controls.[34]

Bempedoic acid

ETC-1002 (bempedoic acid), a small molecule that is orally administered, is a prodrug rapidly metabolized by an endogenous liver acyl-CoA-synthetase and converted to a coenzyme A derivate. ETC-1002-CoA is the active metabolite responsible for the inhibition of ATP

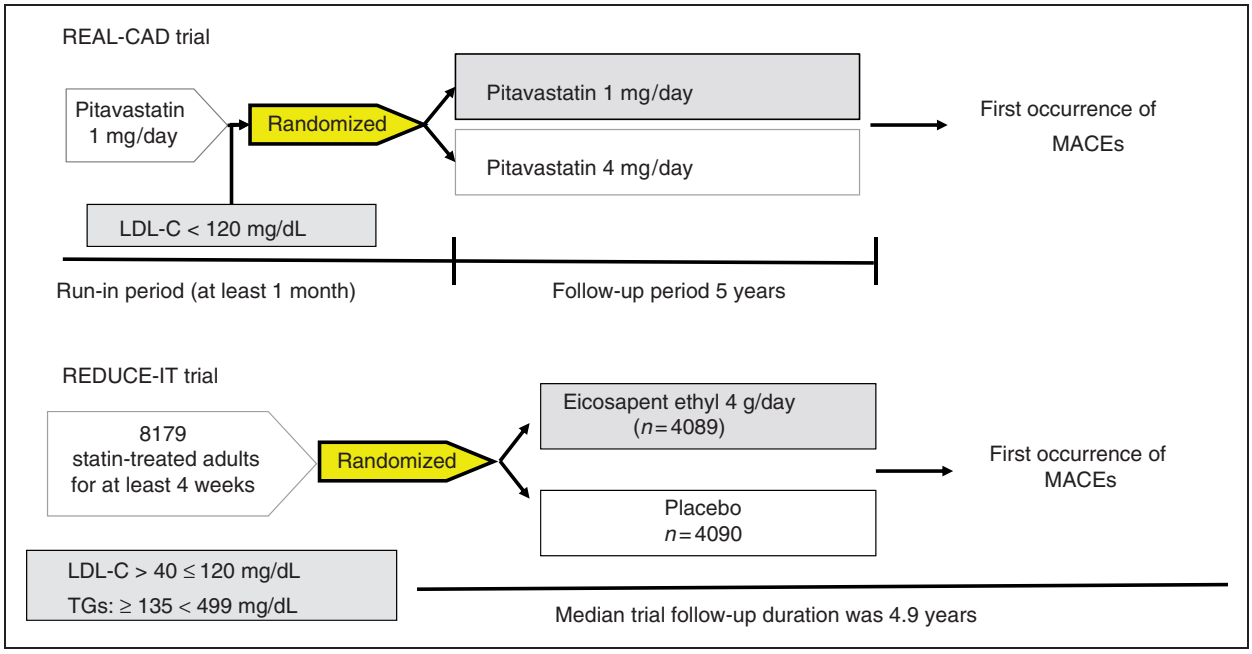


Figure 2. Scheme of the two outcomes trials with pitavastatin (REAL-CAD) and eicosapent ethyl (REDUCE-IT).
MACE = composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, unstable angina.
LDL-C: low-density lipoprotein cholesterol; MACE: major adverse cardiovascular event; TG: triglyceride

Table 1. LDL lowering agents: pitavastatin and bempedoic acid.

Pitavastatin: outcomes trial

REAL-CAD trial	Duration	Study description	LDL-C lowering (absolute changes)
OUTCOMES study	Four years	13,054 patients with cardiovascular artery disease randomized pitavastatin 1 mg or pitavastatin 4 mg daily	−14.7 mg/dL by pitavastatin 4 mg −19% MACEs reduction by pitavastatin 4 mg with an NNT of 63 over five years

Bempedoic acid: phase 3 and outcomes clinical trials

CLEAR trials	Duration (weeks)	Study description	LDL-C lowering (absolute changes)
Tranquility	12	ASCVD patients with a history of statin intolerance requiring additional LDL-C lowering (LDL-C ≥ 100 mg/dL); dose 180 mg	–28.5%
Serenity	24	Statin intolerant patients with inadequately controlled LDL-C; 180 mg	–22% (week 12)
Harmony	52	High-risk ASCVD and HeFH patients with LDL-C ≥ 70 mg/dL; dose 180 mg	−18.1% (week 12); −16.1 (week 24) and −13.6 (week 52)
Wisdom	52	Patients at high CVD risk already at maximally tolerated statin regimen requiring additional LDL-C lowering (LDL-C ≥ 100 mg/dL); dose 180 mg	−17.4% (week 12) maintained for 52 weeks 2% reduction in MACEs (week 52)
Outcomes	4.7 years	Enrolling about 12,600 ASCVD or at high CVD risk statin intolerant patients	Completion expected 2020

ASCVD: atherosclerotic cardiovascular disease; CLEAR: Cholesterol Lowering via BEmpedoic Acid, an ACL-inhibiting Regimen; CVD: cardiovascular; HeFH: heterozygous familial hypercholesterolaemia; LDL-C: low-density lipoprotein cholesterol; MACE: major adverse cardiovascular event; NNT: number-needed-to-treat; REAL-CAD: Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease [AQ34]

citrate lyase (ACLY) reducing the production of cytosolic acetyl-coenzyme A, a precursor of the mevalonate pathway of cholesterol biosynthesis.[35] ACSVL1 is absent in skeletal muscle and thus provides a mechanistic basis for ETC-1002 to potentially avoid the myotoxicity associated with statin therapy. Conversely, in the liver expressing the converting enzyme, ETC-1002-CoA suppresses cholesterol synthesis, with a compensatory upregulation of LDL.[36] ETC-1002 also activates the adenosine monophosphate-activated protein kinase (AMPK) pathway, which controls the metabolic shift from anabolic to catabolic processes, for example, fatty acid β-oxidation. The ETC-1002 upregulated LDL receptor, decreased plasma LDL-C and attenuated experimental atherosclerosis independently of AMPK.[36]

The safety and efficacy of the long-term use of bempedoic acid, including the occurrence of muscle-related adverse events, have been addressed in the following phase 3 clinical trials: CLEAR (Cholesterol Lowering via BEmpedoic Acid, an ACL-inhibiting Regimen) Tranquility, CLEAR Serenity, CLEAR Wisdom and CLEAR Harmony (Table 1).

CLEAR Tranquility enrolled ASCVD patients on very low dose statins, with a history of intolerance to these agents and who required additional LDL-C lowering (LDL-C ≥ 100 mg/dL). In the run-in phase, patients were given open-label ezetimibe 10 mg daily in a single-blind fashion, or placebo, to confirm tolerance to ezetimibe. Background lipid-modifying therapy was allowed for the duration of the trial. Twelve-week treatment with bempedoic acid led to a 28.5% LDL-C reduction, allowing the majority of patients to reach values ≤100 mg/dL (from a mean of 129.8 mg/dL at baseline to 96.2 mg/dL at week 12). LDL-C lowering was much stronger among those on no-statin or no background therapy (–34.7%) versus those receiving very low-dose statin (–20.5%). A remarkable 32.5% reduction in hs-CRP level from baseline was found in the bempedoic acid arm. Muscle-related adverse events occurred equally across treatment groups.[37]

Over a period of 52 weeks, the safety and efficacy were tested in the CLEAR Harmony controlled trial, enrolling 2230 ASCVD and/or heterozygous familial hypercholesterolaemia (HeFH) patients with LDL-C ≥ 70 mg/dL on a guideline-based statin regimen.[38,39]

Mild-to-moderate adverse events were reported in 78.5% of patients who received bempedoic acid compared with 78.7% in the placebo group. Adverse events classified as cardiac disorders (e.g. death from cardiovascular or non-cardiovascular causes, non-fatal MI) occurred in 10.6% in the bempedoic *vs*. 11.6% in the placebo. Finally, a higher rate of discontinuation was recorded in the bempedoic acid arm, that is, 10.9% *vs*.7.1%. Although a greater number of deaths was found in patients given bempedoic acid (0.9% *vs*. 0.3%), no between-group differences were found in the incidence of cardiovascular events or mortality.[40]

As a secondary endpoint, bempedoic acid, added to a moderate-intensity or high-intensity statin regimen, reduced LDL-C by −18.1% (week 12), −16.1% (week 24) and −13.6% (week 52). In the intent-to-treat analysis at week 12, these reductions were maintained whether or not LDL was ≥100 or <100 mg/dL. Overall, these decrements in LDL-C were associated with an incidence in diabetes mellitus of 3.3% in the bempedoic acid versus 5.4% (placebo). Over the 52-week study period, median basal hs-CRP levels (1.49 mg/L) were reduced by −22.4% (week 12), −16.4% (week 24) and −14.4% (week 52) over placebo.[40]

The CLEAR Wisdom trial evaluated the efficacy and safety of bempedoic acid in patients with pre-existing ASCVD risk and/or HeFH, already at maximally tolerated statin doses and requiring additional LDL-C lowering. Bempedoic acid led to an absolute −17.4% reduction on LDL-C, maintained for 52 weeks; at week 12, hs-CRP fell by 19% from baseline (–9.3% *vs*. placebo). Concerning clinical endpoints: three-point MACEs were 8.2% (bempedoic acid) *vs*. 10.1 (placebo); four-point MACEs were 5.7% (bempedoic acid) *vs*. 7.8 (placebo); five-point MACEs 6.1% (bempedoic acid) *vs*. 8.2% in placebo. No worsening in glycaemic control was reported in patients with a history of diabetes.[41]

The CLEAR Serenity trial evaluated the LDL lowering activity and tolerability of bempedoic acid in 354 statin intolerant patients with ASCVD and inadequately controlled LDL-C over a period of 24 weeks.[42] After a 12-week treatment, in patients on very low dose statin, other lipid-modifying therapy or no therapy LDL-C, non-HDL-C and hs-CRP fell by 22%, 19% and 28%, respectively. These effects were maintained at week 24. Myalgia occurred in 4.7% of patients given bempedoic acid and in 7.2% of those on placebo.[43]

A large outcome study is ongoing, that is, CLEAR Outcomes, which is enrolling 12,600 patients at high risk of ASCVD who can tolerate less than the lowest approved daily starting dose of statin. Completion is expected in 2020.

Brief summary. Bempedoic acid, besides efficiently lowering LDL-C, has shown excellent tolerability without occurrence of myalgia. This relates to a non-skeletal muscle mediated conversion of inactive to active drug. Bempedoic acid lowers hs-CRP to the same extent as statins.[44] Considering that statin discontinuation leads to a 50% higher risk of coronary events,[45] bempedoic acid may be chosen as a statin replacement (eventually in combination with ezetimibe) for patients needing LDL-C lowering and experiencing muscular side effects. Moreover, the additional LDL lowering of bempedoic acid when added to moderate-intensity statins or maximally tolerated dosages is greater than the 6% reduction expected from doubling the dose of statins.[46] While awaiting the results of the CLEAR Outcomes study, an important contribution was provided by a Mendelian randomization analysis in which inherited variants in the ACLY locus that mimic the effect of an ACLY inhibitor were associated with a significant reduction in major cardiovascular events. Specifically, for each decrement of 10 mg/dL in LDL-C, the ACLY score was associated with a 17.7% and 19.4% reduction in major cardiovascular events and MI, respectively. The combination of both ACLY and HMGCR and ACLY and NPC1L1 scores were associated with a dose-dependent decrease in LDL-C and apoB and major cardiovascular events.[47] There was no genetic association with an increased risk of cancer. Approval for bempedoic acid monotherapy and the combination bempedoic acid/ezetimibe is currently being sought from the Food and Drug Administration and the European Medicines Agency.

TG lowering

High-dose eicosapentaenoic acid

n-3 polyunsaturated fatty acids (PUFAs) are available in a variety of formulations, ranging from triglycerides, modified phospholipids, ethyl esters of the major omega-3 s, that is, of eicosapentenoic acid (EPA), docosahexaenoic acid (DHA), docosapentenoic acid, in different combinations. Daily doses of 1 g of EPA:DHA in 1.5:1 to 3:1 ratios are the most frequently used regimen,[48] whereas monotherapy with single n-3 PUFAs is gaining interest.

The use of omega-3 fatty acids in cardiovascular prevention has had limited success, although some reports indicate efficacy, that is, the GISSI Study with 1 g of the combination, but the most recent meta-analysis of this therapeutic strategy did not, however, report positive outcomes.[49] Omega-3 fatty acids, particularly EPA, activate the peroxisomal oxidative system in preference to the mitochondrial system, because of the weaker recognition by carnitine palmitoyl transferase. Accordingly, omega-3 fatty acids act as 'fraudulent fatty acids',[50] leading to the classical morphological

changes exerted by peroxisomal proliferator activated receptor α (PPAR-α) agonists.

In the JELIS (Japan eicosapentaenoic acid (EPA) Lipid Intervention Study) trial, hypercholesterolaemic patients (25% with a history of CVD) on stable statin treatment – mainly pravastatin – were randomized to 1.8 g/day high-purity EPA *vs.* placebo.[51] This dose of EPA significantly reduced the relative risk of major coronary events: −19% over a 4.6-year-mean follow-up.[52] The findings of this study suggested that the use of EPA versus a standard EPA/DHA mixture had improved efficacy in decreasing cardiovascular events. In the USA, therefore, a formulation of high purity prescription EPA ethyl ester was approved at a daily dose of 4 g daily as an adjunct to diet for the reduction of triglyceride levels in adults with triglyceride levels ≥500 mg/dL. The daily icosapent ethyl 4 g/day increased serum EPA levels in a Western population to a similar extent as in the Japanese patients in the JELIS study.[52] Most cardiovascular outcome trials have been carried out with the classical EPA/DHA formulation, generally with low daily dosing, that is, 1 g/day. Such is the case in two recently completed cardiovascular outcome trials, that is, the ASCEND (A Study of Cardiovascular Events iN Diabetes) in diabetics (1 g/day of n-3 PUFA ethyl esters with an EPA/DHA ratio of 1.2)[53] and the VITAL (Vitamin D and Omega-3 Trial) in a general population (with similar dose and EPA/DHA ratio) also assessing the effects of vitamin D supplementation.[54] Neither of these two studies provided evidence for a lower incidence of cardiovascular events in the group assigned to n-3 PUFAs. The ongoing STRENGTH (Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) study is instead based on Epanova®, a new formulation of purified (non-ethyl-ester) combination of EPA and DHA at a dose per capsule of 850 mg (15–25% EPA, 50–60% DHA). The pharmacokinetics of omega-3 free fatty acids formulation was tested in the ECLIPSE study comparing Epanova® with Lovaza® in a single-dose evaluation; the non-ethyl-ester formulation appears to have greater bioavailability than the omega-3 ethyl ester formulation.[55]

After 2–4 g daily of Epanova in the EVOLVE study, levels of EPA and DHA increased respectively by 267–406% and by 57–72%. Lowering of triglyceride was −26% to −31% and of non-HDL-C −7.5% to −9.6% versus baseline.[56] In the STRENGTH Study 4 g/day of Epanova or a corresponding placebo will be added to a statin regimen in order to assess a beneficial cardiovascular risk reduction.[57] [AQ6]

The efficacy and safety of icosapent ethyl (formerly AMR101) were evaluated in the MARINE (Multi-Center, PlAcebo-Controlled, Randomized, Double-BlINd, 12-week study with an open-label Extension) study. In 229 patients with very high triglyceride (≥500 and <2000 mg/dL), with or without statin therapy, a 12-week administration of icosapent ethyl 4 or 2 g/day was superior to placebo (capsule of light liquid paraffin) in reducing baseline triglyceride. This effect was dose-dependent with absolute changes of −33% and −19.7% in patients on 4 or 2 g, respectively (Table 2 [58]). Restricting analysis to patients with triglyceride ≥750 mg/dL, the drop was more significant, that is, −45.4% and −32.9%, respectively. Of note, a synergistic effect was found in patients on a statin background, that is, −65% with 4 g and −40.7% with 2 g icosapent ethyl.[59] Improvements were also found in lipoprotein particle concentration and size, for example, large VLDL (–27%), total LDL (–16%), small LDL (–26%) and total HDL (–7%), with no changes in overall sizes of LDL or HDL particles.[60] The 4 g dose also reduced hs-CRP by −36%,[61], a paramount effect reached in patients with a statin background and metabolic syndrome (–78%).[62] No changes in oxidized-LDL, ICAM-1 and interleukin (IL)-6 levels were seen.[61] Similar results were obtained in the ANCHOR (Effect of AMR101 (4 g) on Triglyceride Levels in Patients on Statins With High TG Levels (≥200 and <500 mg/dL)) study, in which nuclear magnetic resonance spectroscopy was used to measure lipoprotein particle concentration and size.[63] Compliance was carried out by analysis of red blood cell (RBC) fatty acids and it allowed the detection of a possible relationship with biological activity. After 12 weeks, the RBC EPA content rose by 792% in the 4 g/day group and by 402% in the 2 g/day group; arachidonic/EPA ratio was reduced respectively −99% and −88%, thus underlining the remarkable prevalence of anti-inflammatory versus pro-inflammatory fatty acids.[64] [AQ7] [AQ8] [AQ9]

The REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention) trial was aimed to test the hypothesis of cardiovascular risk reduction by icosapent ethyl administration. A total of 8179 patients, 70.7% in secondary prevention, with fasting triglyceride 135–499 mg/dL and LDL-C 41–100 mg/dL, were randomized to either icosapent ethyl 2 g b.i.d. or placebo containing mineral oil, in order to mimic colour and consistency of icosapent ethyl (Figure 2). A total of 4 g icosapent ethyl led to a mean of 183 μg/mL of plasma EPA, that is, very close to that reported in the JELIS study.[65] After a median follow-up of 4.9 years, a composite of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization or unstable angina was reduced by 25% in the icosapent ethyl group versus placebo. The absolute between-group reduction was 4.8% with a NNT of 21 over 4.9 years. Key secondary endpoints were also

Table 2. Triglyceride lowering agents: n-3 fatty acids.

Clinic study	Major findings
High-dose icosapent ethyl	
Phase 3 MARINE (Multi-Center, PlAcebo-Controlled, Randomized, Double-BlINd, 12-week study with an open-label Extension) Follow-up: 12 weeks Subjects: 229	1. TG reduction in the whole cohort: −19.7% (2 g) and −33% (4 g) 2. TG reduction in patients with TG ≥ 750 mg/dL: −32.9% (2 g) and −45.4% (4 g)
Phase 3 REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention) Follow-up: 4.9 years Subjects: 8179	1. MACEs reduction: −25% 2. The occurrence of first and all recurrent major CV events were reduced by −30%: first events fall by −25%, the second ones by −32%, the third ones by −31% and the fourth ones or more by −48% 3. hs-CRP reduction: −37.9%
EPA/DHA formulation, generally with low daily dosing, i.e. 1 g/day	
Phase 3 VITAL (Vitamin D and Omega-3 Trial) Follow-up: 5.3 years Subjects: 25,871	Supplementation with n-3 fatty acids did not result in a lower incidence of major cardiovascular events
Phase 4 ASCEND (A Study of Cardiovascular Events in Diabetes) Follow-up: 7.4 years Subjects: 15,480	In diabetic patients without evidence of cardiovascular disease, n-3 fatty acids supplementation was not superior to placebo in preventing the risk of serious vascular events
Ongoing studies	
RESPECT-EPA (Randomized Trial for Evaluation in Secondary Prevention Efficacy and Combination) EPA: 1.8 g/day Follow-up: five years Subjects: about 3900	Expected completion 2022 (Japan). Patients with chronic coronary artery disease receiving statins are randomized to either a control group (standard treatment) or EPA group Primary endpoint: first occurrence of MACEs
OMEMI (Omega-3 Fatty Acids in Elderly Patients With Acute Myocardial Infarction) EPA 1.8 g/day + DHA Follow-up: 2–4 years Subjects: 1400 NCT01841944	Expected completion 2020 (Norway). To investigate the possible effects of supplementation with 1.8 g/day of n-3 polyunsaturated fatty acids on cardiovascular morbidity and mortality in stable post myocardial infarction patients Primary endpoint: first occurrence of combined total mortality, first event of non-fatal myocardial infarction, stroke and revascularization

Adapted from Botta et al.[58]

CV: cardiovascular; DHA: docosahexaenoic acid; EPA: eicosapentenoic acid; hs-CRP: high-sensitivity C-reactive protein; MACE: major adverse cardiovascular event; TG: triglyceride

reduced by 26% with a NNT of 28 (Table 2). These changes were associated with an 18.3% fall in triglyceride from baseline to one year with an LDL-C rise of 3.1%. Changes in hs-CRP were also found, with a between-group difference, at the last visit, of −37.9%. Subgroup analyses showed that, for primary and secondary endpoints, the superiority of icosapent ethyl was consistent, irrespective of triglyceride lowering, thus leaving open questions on some possible pleiotropic effects.[66] Icosapent ethyl reduced total events, that is, the occurrence of first and all recurrent major cardiovascular events, by 30%. Specifically, first events fall by 25%, the second ones by 32%, the third ones by 31% and the fourth ones or more by 48%.[67] Interestingly, a secondary analysis based on baseline triglyceride tertiles showed that icosapent ethyl reduced ischaemic events regardless of triglyceride basal levels, that is, −21% (triglyceride levels ≥81 to ≤190 mg/dl), −20% (>190 to ≤250 mg/dL) and −32% (>250 to <1401 mg/dL).[68]

Concerning safety, the rate of atrial fibrillation was higher in the icosapent ethyl group versus placebo (5.3% *vs.* 3.9%), as was the percentage of peripheral oedema (6.5% *vs.* 5.0%).[66] These data are of great value considering that in a real-world analysis, the average total healthcare cost per patient per month and rate of occurrence of in-patient hospital stay are higher for patients with high triglyceride.[69]

Finally, in the context of atherosclerosis, the ongoing EVAPORATE (Effect of Vascepa on Progression of Coronary Atherosclerosis in Persons with Elevated Triglycerides (200-499) on Statin Therapy) study will determine progression rates of low attenuation unstable plaques under the influence of Vascepa versus placebo (NCT02926027).

Brief summary. In epidemiological, genetic and clinical studies, elevated triglyceride levels have been consistently associated with raised ASCVD risk.[70] However, there is a paucity of triglyceride lowering drugs. The significant cardiovascular risk reduction following high-dose EPA (4 g/day) in the REDUCE-IT study[66] was unexpected. Indeed, although omega-3 fatty acids lower triglyceride levels and may have pleiotropic effects such as reducing plaque instability and proinflammatory mediators of atherogenesis, clinical outcome data before REDUCE-IT were inconsistent.

REDUCE-IT partially confirmed the earlier JELIS study in Japan,[51] indicating high-dose EPA as a novel agent for the prevention of ASCVD in hypertriglyceridaemic patients. Translating the impact of REDUCE-IT findings into clinical practice, a real-world study showed that 17.1% of patients with T2D and acute coronary syndrome may benefit from icosapent ethyl therapy for the risk of residual hypertriglyceridaemia.[71] Another clinical implication is that the favourable effects of icosapent ethyl were partly independent of triglyceride reduction, thus allowing the notion of pleiotropic effects.[72] The possible efficacy of n-3 PUFA supplementation on cardiovascular risk is being tested in the ongoing RESPECT-EPA (Randomized trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy – Statin and Eicosapentaenoic Acid) and OMEMI (Omega-3 Fatty Acids in Elderly Patients With Acute Myocardial Infarction) studies.[73]

PPAR-α modulator – pemafibrate

Pemafibrate (formerly K-877) is the newest member of selective PPAR-α modulators. It stimulates the PPAR-α activity selectivity by introducing a 2-aminobenzoxazole ring and phenoxyalkyl chain into the fibric acid structure. It activates PPAR-α with a greater potency compared with other fibrates, with a lower EC_{50} and a higher degree of selectivity, being >2000-fold more selective for PPAR-α versus either PPAR-γ or PPAR-δ (delta).[74] The selectivity of pemafibrate as a PPAR-α modulator was demonstrated in primary human hepatocytes in which the genes beyond the PPAR-α cascade, for example, those of fatty acid β-oxidation, were up- or down-regulated more robustly compared with fenofibrate.[74]

The unique structural feature of this new drug relies on its Y-shaped frame allowing pemafibrate to occupy all areas of the ligand-binding pocket of the human PPAR-α complex. In particular, compared with fenofibrate, the presence of two additional pharmacophores, that is, aminobenzoxazole and dimethoxybenzene, allows pemafibrate to strongly interact with PPAR-α; this leads to a different size of the ligand-binding pocket, that is, 828Å^3 in pemafibrate-bound and 1163Å^3 in fenofibrate-bound.[75]

The clear definition of efficacy of pemafibrate on the lipid profile, that is, triglyceride reduction and HDL-C increment, in preclinical studies as well as in phase 1 and phase 2 clinical trials, has been previously reviewed.[76] Pemafibrate has been approved in Japan for the treatment of hyperlipidaemias, including the familial phenotypes.

The pharmacokinetic profile is characterized by a slow steady state attainment, stable concentrations being reached on day 2 of repeated administrations (0.1 mg/day), with an absolute bioavailability of 61.5%. After the administration of radiolabelled pemafibrate, 14.5% of radioactivity was recovered in urines and 73.3% in faeces. It is a substrate of a number of cytochromes, mainly CYP2C8, CYP2C9 and CYP3A4, as well as of several efflux and uptake transporters, for example, P-glycoprotein and OATP1B1. It is primarily liver eliminated, whereas fenofibrate, gemfibrozil and bezafibrate have a predominant kidney elimination.[77]

Phase 2 studies. The effectiveness of pemafibrate was evaluated in patients on statins (JapicCTI-121837 and JapicCTI-132067). In patients with residual dyslipidaemia (fasting triglyceride 347–382 mg/dL) and LDL-C levels (116–125 mg/dL) on pitavastatin, pemafibrate (0.1, 0.2 and 0.4 mg/day) led to an absolute triglyceride reduction in the range of −46.1% to −53.4%. Furthermore, pemafibrate, as an add-on therapy, significantly raised HDL-C (range: +12.7% to +19.7%) and apoA-I (range: +1.5% to +6.6%) and lowered non-HDL-C (range: −10.7% to −13.1%) and ApoB (range: −7.9% to −8.6%). Similar percentage changes in triglyceride, that is, −50%, were found when pemafibrate was given in combination with any statin. The incidence of adverse events was similar across all groups. The proportion of patients experiencing elevated alanine aminotransferase (ALT), creatine kinase and serum creatinine were comparable.[78] The above described studies reported an increment in the levels of fibroblast growth factor 21, a metabolic regulator of blood glucose and lipid homeostasis, upon pemafibrate treatment.[78]

Phase 3 studies. Pemafibrate was more effective than placebo in reducing fasting triglyceride among 167 eligible

participants with T2D (glycated haemoglobin (HbA1c) ≥6.2% and fasting triglyceride ≥150 mg/dL) enrolled in the JapicCTI-142412 trial. Twenty-four weeks of pemafibrate treatment (0.2 or 0.4 mg daily) led to a significant 45% triglyceride reduction, with no dose-dependent effect. Fasting triglyceride ≤150 mg/dL was achieved by 81.5% and 70.9% of patients on the 0.2 and 0.4 mg doses, respectively. In addition, non-HDL-C, remnant lipoprotein cholesterol, apoB-100, apoB-48, and apoCIII levels were reduced with a concomitant rise of HDL-C and apoA-I. In particular, pemafibrate raised the cholesterol content of medium, small and very small HDL particles relative to very large and large particles. While plasma LDL-C concentration was not significantly altered, pemafibrate was associated with significant increments of large LDL and drop of small and very small particles. Modest and non-statistically significant changes were found for fasting glucose, insulin, glycated albumin and HbA1c. All groups displayed comparable rates of adverse events, for example, increases in serum creatinine and liver enzymes[79] (Table 3). The long-term safety and efficacy of pemafibrate were the aim of the PROVIDE study (PemafibRate study tO Validate a 52-week efficacy and safety In patients with type 2 Diabetes comorbid with Elevated triglyceride levels), representing the extension of the above described trial. Patients originally allocated to placebo were switched to pemafibrate 0.2. mg and over 52 weeks of treatment triglyceride levels fell by −48.2% in the placebo/fenofibrate group, by −42.3% with pemafibrate 0.2 mg and by −46.4% with pemafibrate 0.4 mg. HDL-C and non-HDL-C as well as total cholesterol were improved by drug administration.[80]

The non-inferiority of pemafibrate as monotherapy, relative to micronized fenofibrate was tested in the JapicCTI-121764 trial, randomizing 526 patients (489 completed the study) with triglyceride ≥200 mg/dL and HDL-C <50 mg/dL for men or <55 mg/dL for women. A 12-week treatment with pemafibrate reduced

Table 3. Triglyceride lowering agents: fibrates.

Pemafibrate

Clinic study	Major findings
Phase 2 Follow-up: 12 weeks Subjects: 188	1. TG reduction: range −46.1% to −53.4%
Phase 2 Follow-up: 24 weeks Subjects: 423	1. TG reduction: range −46.8% to −50.8%
Phase 3 (JapicCTI-142412; clinicaltrials.jp) Follow-up: 24 weeks Subjects: 167 with T2D	1. TG reduction: −45% 2. Reduced non-HDL-C 3. Raised HDL-C
Phase 3 PROVIDE (PemafibRate study tO Validate a 52-week efficacy and safety In patients with type 2 Diabetes comorbid with Elevated triglyceride levels) Follow-up: 52 weeks Subjects: 166 with T2D	1. TG reduction: −48.2% (placebo up to week 24 and thereafter switched to pemafibrate 0.2 mg up to week 52) 2. TG reduction: −42.3% (pemafibrate 0.2 mg) and −46.4% (pemafibrate 0.4 mg)
Phase 3 (JapicCTI-121764; clinicaltrials.jp) Follow-up: 12 weeks Subjects: 489	1. TG: −46.3% (0.1 mg/day), −46.7% (0.2 mg/day) and −51.8% (0.4 mg/day) *vs.* −38.3% (fenofibrate 100 mg/day) and −51.5% (fenofibrate 200 mg/day)
Phase 3 (JapicCTI-142620; clinicaltrials.jp) Follow-up: 24 weeks Subjects: 225	1. TG reduction: −46.2% 2. A further −6.5% TG reduction compared with fenofibrate
On-going phase 3 trial PROMINENT (Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes) – NCT03071692	Outcomes: first occurrence of non-fatal myocardial infarction, non-fatal ischaemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization, and CV death

Adapted from Botta et al.[58]

CV: cardiovascular; HDL-C: high-density lipoprotein cholesterol; MACE: major adverse cardiovascular event; T2D: type 2 diabetes; TG: triglyceride

triglyceride levels in a dose-dependent manner by 46.3% (0.1 mg/day), 46.7% (0.2 mg/day) and 51.8% (0.4 mg/day). Reductions after fenofibrate were 38.3% (100 mg/day) and 51.5% (200 mg/day). At all doses, pemafibrate was more effective versus fenofibrate 100 mg/day, whereas at the daily doses of 0.2 mg and 0.4 mg, pemafibrate was equivalent to fenofibrate 200 mg/day. Adverse events, including liver and kidney laboratory changes, were less frequent than with fenofibrate 200 mg/day.[81] Finally, it is worth mentioning that fenofibrate raised homocysteine levels,[82] whereas pemafibrate had a neutral effect[83] (Table 3).

These findings have been confirmed in the JapicCTI-142620 trial, enrolling 225 patients with triglyceride between 150 and 500 mg/dL and HDL-C <50 mg/dL in men or < 55 mg/dL in women, allocated to a daily dose of 0.2 or 0.4 mg pemafibrate versus fenofibrate. Compared with fenofibrate, pemafibrate treatments, at both doses, reduced triglyceride to a significantly larger extent, that is, −6.5% and −6.2%, respectively. No superiority of pemafibrate versus fenofibrate was found when triglyceride, non-HDL-C, apoB, VLDL cholesterol, HDL-C and apoA-I levels were considered. The apoA-II rises with pemafibrate (0.2 mg/day and 0.4 mg/day) were significantly larger versus fenofibrate. The incidence of adverse reactions in the pemafibrate groups was 2.7% and 6.8%, respectively, versus 23.7% with fenofibrate[84] (Table 3).

Outcome study. The effectiveness of pemafibrate is being evaluated in the on-going cardiovascular outcomes trial PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes). This study will enrol close to 10,000 patients with T2D (two-thirds in secondary prevention and one-third in primary prevention), fasting triglyceride ≥200 to <500 mg/dL, HDL-C ≤ 40 mg/dL on moderate/high intensity statin (atorvastatin ≥40 mg, rosuvastatin ≥20 mg, simvastatin ≥40 mg or pitavastatin ≥4 mg) or with LDL-C ≤ 70 mg/dL. For statin intolerant patients an LDL-C ≤ 100 mg/dL is allowed. The objective will be that of evaluating the superiority of pemafibrate (0.4 mg/day) in raising time to the first occurrence of non-fatal MI, non-fatal ischaemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization, and cardiovascular death. Changes in lipid end-points including apoA-I, apoCIII, apoE and non-fasting remnant cholesterol are listed as secondary outcomes. Considering that the PROMINENT study will continue until 1092 participants, of whom at least 200 are women, will experience an event, an average follow-up of 3.5 years is expected.[85]

The rationale of this study lies on the evidence that, despite LDL-C[86] being unquestionably the main arterial disease risk factor, inflammation[87] and hypertriglyceridaemia[88] have garnered increasing attention. The cholesterol content of triglyceride-rich lipoproteins, that is, that of remnant cholesterol, would appear to be the cause of atherosclerosis and CVD rather than raised triglyceride per se. Smaller remnant lipoproteins undergoing triglyceride hydrolysis by lipoprotein lipase can enter the sub-intimal space, being taken up directly by macrophages, leading to foam cell formation.[88]

The efficacy of fibrates on cardiovascular prevention have been disputed, mainly based on the lack of appropriately selected patients.[89] Long-term re-evaluation of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study confirmed that fenofibrate efficiently reduced CVD in carriers of dyslipidaemia, defined as triglyceride >204 mg/dL and HDL-C < 34 mg/dL, whereas neutral effects were found when the entire patient cohort was considered (hazard ratio: 0.93; 95% CI: 0.83–1.05).[90] The same conclusion was reached in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial, reporting that subjects with marked dyslipidaemia, that is, triglyceride ≥204 mg/dL and low HDL-C, were those who benefitted the most by fenofibrate, with a 27% relative risk reduction (NNT = 23).[91]

Finally, in an effort to understand possible cardioprotective effects of pemafibrate, a recent study demonstrated that the drug improves the cholesterol efflux capacity of HDLs obtained from fasting blood samples of patients with dyslipidaemia, defined as fasting triglyceride >150 mg/dL and HDL-C < 50 mg/dL (men) and <55 mg/dL (women). HDL-C, apoA-I, HDL_3-C and pre-β1 HDL levels were also raised.[92]

Brief summary. Pemafibrate is a novel addition to the field of TG regulating agents. This agent offers the novelties of the selective PPAR-α modulator concept, that is, of a selective activity on PPAR-α, different from available fibrates, non-selectively acting on two or more PPARs,[77] as well as of very daily low doses (0.2–0.4 mg).[75] The HDL-C rise after pemafibrate goes together with increases of medium, small and very small HDL particles, with a more powerful cholesterol mobilizing activity.[92] Concerning safety, in a head-to-head comparison with fenofibrate, pemafibrate decreased alanine aminotransferase and gamma-glutamyltransferase levels, whereas fenofibrate raised both enzymes. The increments of serum creatinine were smaller in patients on pemafibrate compared with those on fenofibrate;[84] this trend was similar for changes in plasma homocysteine.[83] A large ongoing study in appropriately selected individuals will most likely provide better data, addressing the issue of clinical cardiovascular prevention.[85]

A wide spectrum of lipid regulating agents

Gemcabene

Gemcabene calcium is the monocalcium salt of a dialkyl ether dicarboxylic acid and represents a new class of lipid regulating compounds, having two terminal gem-dimethyl carboxylate moieties. In studies in rats, gemcabene reduced LDL-C, triglyceride and apoC-III levels, raised HDL-C and showed increased hepatic peroxisomal enzyme activities.[93] However, the apparent mechanism of action, with regard to direct PPAR activation, was surprisingly dissimilar from fibrates, known to directly activate PPAR-α, when assessed in mouse, rat or human PPAR transactivation assays. Indeed, compared with classical fibrates or PPAR-α agonists, gemcabene exerted little or no PPAR-α activation at the highest concentration tested (300 μM), and essentially no PPAR-γ agonist activity at this same concentration. These investigations used known comparative reference PPAR agonists that showed expected results.[93]

The earliest study also indicated that gemcabene accelerates ^{125}I-labelled VLDL apoB disappearance, reducing triglyceride production and elevating the ratio of post-heparin hepatic to lipoprotein lipase activities.[94] These earlier and more recent investigations have provided limited information on mechanism/s, suggesting that these are most likely related to a general activity on de novo cholesterol and triglyceride synthesis, associated with reduced hepatic apoC-III mRNA levels. This may result in increased VLDL remnant uptake and consequently lower LDL-C levels. Additional studies clearly demonstrated an anti-inflammatory profile, associated with a lowered expression of the hs-CRP gene regulating mechanisms.[95]

In view of the significant activity of gemcabene on liver lipids and inflammation, a specific study addressed the anti-inflammatory, lipid altering and cell signalling genes in an animal model of non-alcoholic fatty liver disease (NAFLD). In the STAM™ murine model of NAFLD, gemcabene significantly down-regulated liver mRNA markers of inflammation, lipogenesis, lipid modulation and fibrosis, thus presenting this agent as of potential interest in the management of this very frequent human disease.[96]

Gemcabene thus offers an effective treatment for a wide range of hyperlipidaemias, exerting both a cholesterol and triglyceride reduction, with an additional apparent effectiveness against NALFD, a disorder occurring in more than 25% of the adult population in the Western world.[97] Combined activity on plasma and liver lipid levels and inflammatory markers makes the potential efficacy profile of this agent of interest in a variety of clinical conditions.

The drug, initially developed by Parke-Davis/Warner-Lambert, then by Pfizer, was licensed to Gemphire Therapeutics Inc. for further development in 2011. Gemcabene has been tested clinically since the early 2000s and 10 phase II studies (six in dyslipidaemias) have been conducted. During this time, gemcabene has been administered to over 1100 healthy subjects and patients and has been well tolerated at doses up to 900 mg daily for up to 12 weeks.

The efficacy of gemcabene was tested in a phase 2 double-blind, randomized, dose–response (placebo, 150, 300, 600 or 900 mg) study enrolling 161 patients with HDL-C < 35 mg/dL and triglyceride ≥200 or <200 mg/dL. Within the ≥200 mg/dL triglyceride stratum, the lowest doses, that is, 150 and 300 mg, reduced triglyceride by 27% and 39%, respectively and apoCIII by 23% and 31%; HDL-C was raised by 18% and 12%, respectively. LDL-C dropped by 15–25% only at the highest doses, that is, 600 and 900 mg, irrespective of basal triglyceride levels. Of note, the only dose dependent effect was on non-HDL-C, leading to a stepwise decrement of −1.6% (150 mg), −9.4% (300 mg), −10.9% (600 mg) and −16.3% (900 mg) in the triglyceride <200 mg/dL stratum, with slightly greater dose dependent reductions of non-HDL-C in the triglyceride 200 mg/dL stratum.[98]

In an eight-week double blind, placebo controlled, randomized trial in men and post-menopausal women with LDL-C >130 mg/dL, on stable high intensity statins, a mean LDL-C reduction of 27.7 ± 4.23% ($p < 0.001$) with 900 mg/day was reported. There was a modest activity on triglyceride (–14.6%, $p < 0.09$) and apoB was reduced by 17.2%. The most remarkable finding was a dramatic reduction of hs-CRP levels, that is, −26.1% and −53.9% in the 300 mg and 900 mg treatment groups, respectively.[99]

An investigator initiated, phase 2, proof-of-concept study, testing the preliminary efficacy and safety of gemcabene (300 mg) in children with established NAFLD incompletely treated by lifestyle changes, has been stopped early. The first three patients who underwent 12 weeks of treatment had increasing weight and a rise in liver fat content, with increased ALT noted in two subjects (NCT03436420).

Another phase 2a study (NCT03508687) is still ongoing with the aim to assess the efficacy and safety of two dosing regimens (300 and 600 mg) of gemcabene in patients with familial partial lipodystrophy, elevated triglyceride and non-alcoholic steatohepatitis. To date, there have been no safety concerns.

Gemcabene has been also tested in homozygous familial hypercholesterolaemia (HoFH) patients (COBALT-1 phase 2 trial) on a variety of background lipid lowering therapies, including the highest statin and/or ezetimibe doses and/or PCSK9 inhibitors. Patients were followed with dosages escalating from 300 mg to 600 mg and then 900 mg daily, for a total

duration of 12 weeks. Optimal results were observed with gemcabene 600 mg daily, that is, mean LDL-C reduction of 93 mg/dL for a population with baseline levels of 351 mg/dL. At this same dose, gemcabene lowered non-HDL by −27.2%, apoB by −24.8%, and apoE by −23.0%.[100] Further ongoing trials will evaluate (i) the LDL lowering activity of gemcabene as add-on therapy on top of high- and moderate-intensity statins in HeFH and ASCVD patients (ROYAL-1 study) and (ii) the triglyceride reduction in severely hypertriglyceridaemic patients (INGIGO-1 trial).

Overall, the mechanism of gemcabene for LDL-C reduction is not completely understood. However, preclinical studies have shown that gemcabene reduces acetate incorporation into cholesterol, lowers apoC-III hepatic mRNA and plasma levels and hepatic sulphatase 2 mRNA levels and raises VLDL clearance.[94,96,101,102] The reduction in sulphatase 2 may enhance hepatic Syndecan-1, also known as the VLDL remnant receptor, activity.[103,104] The reduction in plasma triglyceride in diabetic mice correlates to the inhibition of both sulphatase 2 and apoC-III mRNA levels.[101] Gemcabene's enhanced clearance of VLDL remnants may reduce systemic LDL production and partly lower LDL-C levels.

Brief summary. Patients with combined forms of dyslipidaemia are most frequently treated with drug combinations, which increased the potential occurrence of adverse interactions.[105] Gemcabene lowers both cholesterol and triglyceride by a mechanism of action not linked to agonist or antagonist activity on the PPAR-α receptors.[93] Gemcabene has a potent effect in lowering hs-CRP by a complex mechanism, primarily by inhibiting IL-6 and IL-1β induced production of CRP.[95]

HDL regulators

The potential role of HDL in the prevention and treatment of ASCVD has been extensively investigated in recent years. The failure of HDL elevations, from niacin to CETP inhibitors, as well as the uncertainties on the genetic link between HDL-C levels and cardiovascular risk, have not given support to the HDL raising hypothesis.[106] The availability of a newer CETP antagonist and the unique approach provided by probucol as a stimulator of reverse cholesterol transport are, however, worthy of consideration.

CETP inhibition

For many years, the pharmacological inhibition of CETP has been pursued as a therapeutic tool to raise HDL-C. Several pharmacological strategies have been designed to antagonize the activity of CETP, including antisense DNA technology, monoclonal antibodies, anti-CETP vaccines and small molecule inhibitors.[107] While CETP antagonism has resulted in significant, albeit moderate, reductions of cardiovascular events in at least one major long-term study (REVEAL Study),[15] other inhibitors, that is, torcetrapib, dalcetrapib and evacetrapib, have not led to a similar conclusion.[15] In particular, a major drawback for the clinical use of anacetrapib may be the unique pharmacokinetic profile. Detectable concentrations of anacetrapib were found in plasma 2.5–4 years after the last drug dose, associated with modest HDL-C elevations. This finding is likely a consequence of a long-term accumulation of drug in adipose tissue after one year of treatment, as also reported in mice.[16]

The last survivor of this class of drugs is the CETP inhibitor TA-8995 (formerly AMG-8995), a less lipophilic compound. The phase 2 trial NCT01970215, evaluating the efficacy of TA-8995 on HDL and LDL-C, enrolled 337 patients with LDL-C between 2.5 mmol/L and 4.5 mmol/L, HDL-C between 0.8 mmol/L and 1.8 mmol/L and triglyceride levels < 4.5 mmol/L. Patients were randomly assigned to different doses of TA-8995, that is, 1, 2.5, 5 and 10 mg/day, alone or on top of statins, that is, 20 mg atorvastatin or 10 mg rosuvastatin. In the group receiving TA-8995 monotherapy, the 12-week treatment resulted in a 45.3% LDL-C lowering, reaching −68.2% in patients given 10 mg TA-8995 plus atorvastatin 20 mg. A similar trend was found in the arm receiving 10 mg TA-8995 plus rosuvastatin 10 mg (−63.3%). HDL-C levels were raised in a dose-dependent manner, that is, +75.8% (1 mg), +124.3% (2.5 mg), +157.1% (5 mg) and +179.0% in those on 10 mg monotherapy, no further improvement occurring with statin addition. No serious adverse events were observed.[17] When the major antiatherogenic effects of HDL-C were evaluated, that is, the ability to remove excess cholesterol from arterial wall macrophages, TA-8995 raised total, non-ATP-binding cassette transporter (ABCA1)- and ABCA1-specific cholesterol efflux capacity as well as preβ-1 HDL.[108] A cardiovascular clinical outcomes trial will be needed to determine whether these effects will translate into a reduction of ASCVD events.

Brief summary. Although epidemiological and clinical studies link low levels of HDL with an increased cardiovascular risk, a direct causal role of HDL in cardiovascular disease remains controversial. While inhibition of the reverse cholesteryl ester transfer system, controlled by CETP, potently raises plasma HDL-C levels, the clinical outcome trials reported have been negative.[109] The one exception was with anacetrapib, which provided a significant, albeit limited (–9%), reduction in cardiovascular events in a secondary prevention setting against optimal statin therapy.[110]

Finally, in the era of genome-wide association study, data from the Dal-GenE trial, testing the cardiovascular preventive effect of dalcetrapib in acute coronary syndrome patients – carriers of the AA genotype at rs1967309 in the ADCY9 gene – are eagerly awaited[16] also in consideration of the failure of the same genotype in demonstrating any beneficial effect upon evacetrapib[111] or anacetrapib treatment.[112]

Probucol raises reverse cholesterol ester transport: clinical evidence of cardiovascular protection

Probucol, a bisphenol compound, providing a still unique approach to cardiovascular prevention, was synthesized as an antioxidant.[113] After the description of its cholesterol lowering properties, probucol has been used for patients with hypercholesterolaemia in Japan since 1985. Owing to reduced serum HDL-C levels and to possible -QT interval prolongation or occurrence of ventricular arrhythmias, in 1995, probucol was withdrawn in the USA. However, the clinical benefit of probucol has been supported by a significant number of scientific findings in more recent years, leading to the development of some analogues. Probucol activity is characterized by a 20% reduction of LDL-C,[114] by a mechanism independent of the LDL receptor,[115] and a reduction of HDL-C by 30%.[114] In spite of this paradoxical effect on HDL in patients with familial hypercholesterolaemia probucol enhances the regression of Achilles tendon xanthomas and xanthelasmas. These effects were positively related to probucol-induced decrease in HDL-C.[116] Thus, probucol may exert its anti-atherogenic properties by raising lipid-poor preβ1-HDL formation, involved in cellular cholesterol efflux, and by the activation of hepatic CETP and scavenger receptor class B type I with a consequent stimulating reverse cholesterol transport.[117–119] Although probucol blocks ABCA1 mediated cell cholesterol efflux, most likely the end result in vivo may not be a definite reduction of ABCA1 functionality, being compensated by a rise in hepatic endothelial lipase expression[120] and in ABCA1 protein expression, a mechanism mediated by probucol metabolites.

Clinical studies on the effects of probucol on xanthomas, restenosis after percutaneous coronary intervention (PCI) and atherosclerosis have been recently reviewed.[121] Briefly, in the PQRST (Probucol Quantitative Regression Swedish Trial)[122] probucol led to a reduction of both LDL-C and HDL-C by 12% and 24%, respectively. In these hypercholesterolaemic patients either symptomatic or asymptomatic for femoral atherosclerosis, no significant changes in lumen volume were found. This result can be probably explained today by the fact that changes in atheroma volume may occur without changes in lumen due to vessel remodelling. The MVP (MultiVitamins and Probucol) trial[123,124] tested the anti-restenotic effects of probucol after PCI. LDL-C was lowered by 17.6% in patients on probucol, by 16.8% in those on probucol + multivitamins and by 14.8% in the placebo group. HDL-C dropped by 17.6% upon probucol administration and by 31.3% in probucol + multivitamins versus +0.9% in the placebo arm. The stenosis rates per segment were 20.7% in the probucol group, 28.9% in the combined-treatment group and 38.9% in the placebo. The FAST (Fukuoka Atherosclerosis Trial) investigated the effects of probucol on the reduction of carotid intima-media thickness (IMT) and incidence of cardiovascular events in asymptomatic patients with hypercholesterolaemia.[125] In a head-to-head comparison with pravastatin (10 mg), LDL-C fell by 36% with pravastatin and by 29% with probucol, together with a HDL-C reduction of 30% with this latter. Both treatments led to a similar reduction rate in carotid IMT (−13.9%) and a significantly lower incidence of cardiovascular events was observed in the probucol group (2.4% *vs*. 4.8% in the pravastatin group, $p < 0.001$).

The effect of probucol on coronary atherosclerosis associated events in HeFH patients was tested in the POSITIVE (Probucol Observational Study Illuminating Therapeutic Impact on Vascular Events) study. In this prospective study, the incidence of cardiovascular events in secondary prevention was 27.0% in the probucol group and 64.3% in patients who were not exposed. No differences were found in primary prevention because the LDL-C levels were nearly 30 mg/dL higher in the probucol-treated arm versus control.[126] Similar results were reported in patients who underwent complete revascularization (PCI and/or bypass surgery).[127] The PICASSO (Prevention of Cardiovascular Events in Asian patients with Ischemic Stroke at High risk of Cerebral Haemorrhage) study evaluated efficacy and safety of cilostazol versus aspirin, with and without probucol, in patients with ischaemic stroke and a high risk of haemorrhage.[128] Patients were randomized to oral cilostazol, aspirin, cilostazol plus probucol, or aspirin plus probucol. In the probucol groups the incidence of vascular events was reduced by 31% (hazard ratio: 0.69; 95% CI: 0.50–0.97). No statistical differences were found for cerebral haemorrhages: hazard ratio: 0.65; 97.5% CI: 0.27–1.57; $p = 0.55$ (probucol versus non-probucol groups).

Concerning probucol analogues, experimental work shows that elsibucol has antioxidant, anti-inflammatory and antiproliferative properties and reduced proliferation of vascular smooth muscle cells, oxidative stress, VCAM-1 expression and macrophage infiltration into injured arteries. No clinical data are available.[129] Succinobucol, which possesses anti-inflammatory and

antioxidative activities, was tested in the CART-1 (Canadian Antioxidant Restenosis Trial) study versus probucol.[130] Both drugs reduced restenosis after PCI, although prolongation of the QTc interval was more frequent with probucol. In the following CART-2 study, regression of coronary atherosclerosis by succinobucol was demonstrated.[131] The ARISE (Aggressive Reduction of Inflammation Stops Events) trial, enrolling 6144 patients with recent onset of acute coronary syndrome, showed no significant effects of succinobucol on MACEs; conversely, the composite secondary endpoints of cardiovascular death, cardiac arrest, MI or stroke occurred less frequently versus placebo (hazard ratio: 0.81; 95% CI: 0.68–0.98). Succinobucol raised LDL-C and systolic blood pressure, and decreased HDL-C and glycated haemoglobin. An elevation of new-onset atrial fibrillation (hazard ratio: 1.87; 95% CI: 1.67–2.09) led to discontinuation of clinical development.[132]

Brief summary. The regulation of HDL-C remains an enigmatic therapeutic target.[121] Therapeutic increase in HDL flux has a greater anti-atherogenic effect than increasing HDL concentration alone.[133] Data from the PROSPECTIVE (Probucol Trial for Secondary Prevention of Atherosclerotic Events in Patients with Prior Coronary Heart Disease) study will answer the hypothesis whether or not the addition of probucol to other lipid lowering drugs could prevent cerebrovascular and cardiovascular events in patients with prior coronary events and high LDL-C levels.[134] In the meantime, in patients with ischaemic stroke, the addition of probucol to aspirin or cilostazol could be beneficial in reducing the incidence of cardiovascular events.[128]

Conclusions

The newer drug approaches reviewed offer patients and clinicians wider choices for managing dyslipidaemias with hypercholesterolaemias, where benefits may be clouded by insufficient clinical responses or side effects leading to discontinuation and reduced cardiovascular benefits,[135] the novel cholesterol lowering medications pitavastatin and bempedoic acid have provided clear differential effects compared with available agents.

Elevated triglyceride levels, a common finding in daily clinical practice, identify individuals at higher ASCVD risk, related to a cluster of abnormalities referred to as the metabolic syndrome. Thus, in the context of hypertriglyceridaemia associated residual risk, availability of pemafibrate offers a unique mode of action as a selective PPAR-α activator. Another triglyceride lowering pharmacological approach is the use of the omega-3 icosapent ethyl[66] providing a novel indication for a chemical series as yet not proven to be associated with cardiovascular benefit.[49] The REDUCE-IT study further confirmed that an inappropriate selection of cases with hypertriglyceridaemia or metabolic syndrome may have led to the non-convincing activity of triglyceride lowering medications in secondary prevention trials (FIELD, ACCORD studies). Patients with hypertriglyceridaemia/low HDL may derive greater cardiovascular benefit from triglyceride lowering agents, as suggested by the fenofibrate studies.[90,136]

The elusive target of HDL-cholesterol has been poorly addressed by present day lipid lowering medications and HDL function rather than levels appears to be a most appropriate target.[137] In this area, antagonists of the CETP system have led to dramatic HDL-C elevation, albeit with no clear evidence of improved cardiovascular outcomes.[107] Anacetrapib reduced major vascular events by 9%, but was found to accumulate in adipose tissue, and regulatory approval was not requested. Thus, despite considerable initial promise, CETP inhibition provides insufficient cardiovascular benefit for routine use.[106] Conversely, probucol and derivatives, while lowering HDL levels, appear to improve HDL function and reduce inflammation.[121]

The new agents reviewed afford further options for treating patients with dyslipidaemias in a field plagued with problems of poor adherence/low achievement of targets.[138,139] For these agents, cost-effectiveness analysis is certainly more favourable[140] compared with agents of biosynthetic origin, for example, the case of PCSK9 inhibitors, for which the recent American guidelines support use in high-risk patients only if the cost/benefit ratio is favourable.[19]

Limitations in the real-world

As of today, the use of pitavastatin has had limited impact on the European market.[141] Use has been limited owing to the low-cost availability of generic statins. In view of the low dose and reduced drug–drug interaction risk, use may be of interest for patients with multiple drug treatments. Despite the well-recognized triglyceride lowering effect, the European Medicine Agency has not recommended use of omega-3 PUFAs in the secondary prevention of CVD,[142] reversing the authorizations granted over the last two decades permitting these products to be marketed at a dose of 1 g per day for reducing cardiovascular disease. The positive results of the REDUCE-IT trial with EPA may lead to a renewed approval. Pemafibrate is approved only in Japan[143] and, at present, probucol is available only in Eastern nations (Japan, China, Taiwan, Korea and the Philippines), having been withdrawn in the USA and other Western nations.

Future directions

The degree of advantage that the new analysis of REDUCE-IT reveals is quite large, especially considering that this is an additional benefit on top of what statin and other therapies have already provided. Moreover, owing to a finding that icosapent ethyl also reduces ischaemic events in patients with triglyceride $\geq$81 to $\leq$190 mg/dL will possibly redefine the meaning of 'normal' triglyceride values.[68] Thus, clinicians may consider treating high-risk patients with diabetes and dyslipidaemia with high-dose EPA, although cost implications need to be considered.[71] In this context, a cost-effectiveness analysis of the JELIS study showed that EPA + statin combination therapy has an acceptable cost-effectiveness for secondary prevention, but not primary prevention, of CVD patients with hypercholesterolaemia in Japan.[144] This approach might merit consideration also in HIV+ patients often displaying hypertriglyceridaemia with reduced HDL-C and frequently difficult drug handling in daily practice.[145] Finally, in order to achieve LDL-C target levels in high risk ASCVD patients, adding new drugs like bempedoic acid, more cost-effective than PCSK9 inhibitors, may be envisioned as an adjunct to existing management algorithms, as second- or third-line agents, similar to ezetimibe and bile acid sequestrants.[146]

Author contribution

CRS, GFW and MR conceived the topic and wrote the manuscript. AC conceived the topic and critically revised the manuscript. MFG took care of reproducing tables and figures. SY critically revised the manuscript and edited the sections pertaining to pitavastatin, pemafibrate and probucol. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CRS, MFG and MR have nothing to declare. AC received honoraria from AstraZeneca, AMGEN, Sanofi, Recordati, Novartis, MSD, Mediolanum, DOC, Mylan and Pfizer. SY received honoraria from Otsuka, Kowa, MSD, Astellas-Amgen Biopharma, Sanofi, and research grant from MSD, Bayern, Boehringer Ingelheim, Takeda, Ono, Astellas, Tanabe-Mitsubishi, Kyowa Medex, and Rohto. GFW speakers bureau Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Sanofi-Aventis, Servier and Valeant; consultant to Abbott Vascular, Akcea, Amgen, Daichii Sankyo, Esperion, Lilly, MSD, Resverlogix, Sanofi-Aventis; grants from Sanofi and Valeant

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Burnett JR and Hooper AJ. PCSK9 - a journey to cardiovascular outcomes. *N Engl J Med* 2018; 379: 2161–2162.
2. Kersten S. Angiopoietin-like 3 in lipoprotein metabolism. *Nat Rev Endocrinol* 2017; 13: 731–739.
3. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: A systematic review and meta-analysis. *JAMA* 2016; 316: 1289–1297.
4. Macchi C, Banach M, Corsini A, et al. Changes in circulating pro-protein convertase subtilisin/kexin type 9 levels – experimental and clinical approaches with lipid-lowering agents. *Eur J Prev Cardiol*. Epub ahead of print 20 February 2019. DOI: 10.1177/2047487319831500 [AQ10].
5. Du H, Li X, Su N, et al. Proprotein convertase subtilisin/kexin 9 inhibitors in reducing cardiovascular outcomes: A systematic review and meta-analysis. *Heart*. Epub ahead of print 8 March 2019. DOI: 10.1136/heartjnl-2019-314763.
6. Ference BA, Cannon CP, Landmesser U, et al. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: An analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration. *Eur Heart J* 2018; 39: 2540–2545.
7. Reiner Z. Hypertriglyceridaemia and risk of coronary artery disease. *Nat Rev Cardiol* 2017; 14: 401–411.
8. Sandesara PB, Virani SS, Fazio S, et al. The forgotten lipids: Triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk. *Endocr Rev*. Epub ahead of print 13 October 2018. DOI: 10.1210/er.2018-00184 [AQ11].
9. Nordestgaard BG, Benn M, Schnohr P, et al. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA* 2007; 298: 299–308.
10. Ference BA, Kastelein JJP, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. *JAMA* 2019; 321: 364–373.
11. Nordestgaard BG and Varbo A. Triglycerides and cardiovascular disease. *Lancet* 2014; 384: 626–635.
12. Miller YI, Choi SH, Fang L, et al. Lipoprotein modification and macrophage uptake: Role of pathologic cholesterol transport in atherogenesis. *Subcell Biochem* 2010; 51: 229–251.
13. Watts GF, Ooi EM and Chan DC. Demystifying the management of hypertriglyceridaemia. *Nat Rev Cardiol* 2013; 10: 648–661.
14. Madsen CM, Varbo A and Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: Two prospective cohort studies. *Eur Heart J* 2017; 38: 2478–2486.
15. Tall AR and Rader DJ. Trials and tribulations of CETP inhibitors. *Circ Res* 2018; 122: 106–112.

16. Ferri N, Corsini A, Sirtori CR, et al. Present therapeutic role of cholesteryl ester transfer protein inhibitors. *Pharmacol Res* 2018; 128: 29–41.
17. Hovingh GK, Kastelein JJ, van Deventer SJ, et al. Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): A randomised, double-blind, placebo-controlled phase 2 trial. *Lancet* 2015; 386: 452–460.
18. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J* 2016; 37: 2999–3058.
19. Grundy SM, Stone NJ, Bailey AL, et al. 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. *J Am Coll Cardiol*. Epub ahead of print 14 November 2018. DOI: 10.1016/j.jacc.2018.11.003. **[AQ12]**.
20. Fulcher J, O'Connell R, et al.; Cholesterol Treatment Trialists (CTT) Collaboration. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015; 385: 1397–1405.
21. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; 352: 1425–1435.
22. Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: A meta-analysis of statin trials. *J Am Coll Cardiol* 2014; 64: 485–494.
23. Miyauchi K, Kimura T, Shimokawa H, et al. Rationale and Design of Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) trial. *Int Heart J* 2018; 59: 315–320.
24. Corsini A and Ceska R. Drug–drug interactions with statins: Will pitavastatin overcome the statins' Achilles' heel? *Curr Med Res Opin* 2011; 27: 1551–1562.
25. Hu M and Tomlinson B. Evaluation of the pharmacokinetics and drug interactions of the two recently developed statins, rosuvastatin and pitavastatin. *Expert Opin Drug Metab Toxicol* 2014; 10: 51–65.
26. Chamberlin KW and Baker WL. Benefit–risk assessment of pitavastatin for the treatment of hypercholesterolemia in older patients. *Clin Interv Aging* 2015; 10: 733–740.
27. Harada-Shiba M, Kastelein JJP, Hovingh GK, et al. Efficacy and safety of pitavastatin in children and adolescents with familial hypercholesterolemia in Japan and Europe. *J Atheroscler Thromb* 2018; 25: 422–429.
28. Chapman MJ. Pitavastatin: Novel effects on lipid parameters. *Atheroscler Suppl* 2011; 12: 277–284.
29. Aberg JA, Sponseller CA, Ward DJ, et al. Pitavastatin versus pravastatin in adults with HIV-1 infection and dyslipidaemia (INTREPID): 12 week and 52 week results of a phase 4, multicentre, randomised, double-blind, superiority trial. *Lancet HIV* 2017; 4: e284–e294.
30. Ruscica M, Macchi C, Morlotti B, et al. Statin therapy and related risk of new-onset type 2 diabetes mellitus. *Eur J Intern Med* 2014; 25: 401–406.
31. Park JB, Jung JH, Yoon YE, et al. Long-term Effects of high-doSe pitavaStatin on Diabetogenicity in comparison with atorvastatin in patients with Metabolic syndrome (LESS-DM): study protocol for a randomized controlled trial. *Trials* 2017; 18: 501.
32. Taguchi I, Iimuro S, Iwata H, et al. High-dose versus low-dose pitavastatin in Japanese patients with stable coronary artery disease (REAL-CAD): A randomized superiority trial. *Circulation* 2018; 137: 1997–2009.
33. Choi JY, Choi CU, Hwang SY, et al. Effect of pitavastatin compared with atorvastatin androsuvastatin on new-onset diabetes mellitus in patients with acute myocardial infarction. *Am J Cardiol* 2018; 122: 922–928.
34. Mach F, Ray KK, Wiklund O, et al. Adverse effects of statin therapy: Perception vs. the evidence – focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur Heart J* 2018; 39: 2526–2539.
35. Pinkosky SL, Groot PHE, Lalwani ND, et al. Targeting ATP-citrate lyase in hyperlipidemia and metabolic disorders. *Trends Mol Med* 2017; 23: 1047–1063.
36. Pinkosky SL, Newton RS, Day EA, et al. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat Commun* 2016; 7: 13457.
37. Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. *Atherosclerosis* 2018; 277: 195–203.
38. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: 2889–2934.
39. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J* 2016; 37: 2999–3058.
40. Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med* 2019; 380: 1022–1032.
41. Widsom C. Efficacy and safety of bempedoic acid added to maximally tolerated statins in patients with hypercholesterolemia and high cardiovascular risk: The CLEAR Wisdom trial. *American College of Cardiology Congress* 2019 **[AQ13]**.
42. NCT02988115. Evaluation of the efficacy and safety of bempedoic acid (ETC-1002) in patients with hyperlipidemia and statin intolerant (CLEAR Serenity), https://clinicaltrials.gov/ct2/show/NCT02988115 (accessed ▮▮) **[AQ14]**.
43. Laufs U, Banach M, Mancini J, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance, http://abstractsonline.com/pp8/#!/4682/presentation/59949 (2018, accessed ▮▮) **[AQ15]**.
44. Ruscica M, Banach M, Sahebkar A, et al. ETC-1002 (bempedoic acid) for the management of hyperlipidemia:

From preclinical studies to phase 3 trials. *Expert Opin Pharmacother* 2019; ▮▮: 1–13 [AQ16].
45. Serban MC, Colantonio LD, Manthripragada AD, et al. Statin intolerance and risk of coronary heart events and all-cause mortality following myocardial infarction. *J Am Coll Cardiol* 2017; 69: 1386–1395.
46. Nicholls SJ, Brandrup-Wognsen G, Palmer M, et al. Meta-analysis of comparative efficacy of increasing dose of atorvastatin versus rosuvastatin versus simvastatin on lowering levels of atherogenic lipids (from VOYAGER). *Am J Cardiol* 2010; 105: 69–76.
47. Ference BA, Ray KK, Catapano AL, et al. Mendelian randomization study of ACLY and cardiovascular disease. *N Engl J Med* 2019; 380: 1033–1042.
48. Mozaffarian D and Wu JH. (n-3) fatty acids and cardiovascular health: Are effects of EPA and DHA shared or complementary? *J Nutr* 2012; 142: 614S–625S.
49. Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77917 individuals. *JAMA Cardiol* 2018; 3: 225–234.
50. Sirtori CR, Galli C and Franceschini G. Fraudulent (and non fraudulent) fatty acids for human health. *Eur J Clin Invest* 1993; 23: 686–689.
51. Yokoyama M and Origasa H; JELIS Investigators. Effects of eicosapentaenoic acid on cardiovascular events in Japanese patients with hypercholesterolemia: Rationale, design, and baseline characteristics of the Japan EPA Lipid Intervention Study (JELIS). *Am Heart J* 2003; 146: 613–620.
52. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): A randomised open-label, blinded endpoint analysis. *Lancet* 2007; 369: 1090–1098.
53. Bowman L, Mafham M, et al.; ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med* 2018; 379: 1540–1550.
54. Manson JE, Cook NR, Lee IM, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med* 2019; 380: 23–32.
55. Davidson MH, Johnson J, Rooney MW, et al. A novel omega-3 free fatty acid formulation has dramatically improved bioavailability during a low-fat diet compared with omega-3-acid ethyl esters: The ECLIPSE (Epanova((R)) compared to Lovaza((R)) in a pharmacokinetic single-dose evaluation) study. *J Clin Lipidol* 2012; 6: 573–584.
56. Kastelein JJ, Maki KC, Susekov A, et al. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: The EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial. *J Clin Lipidol* 2014; 8: 94–106.
57. Nicholls SJ, Lincoff AM, Bash D, et al. Assessment of omega-3 carboxylic acids in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol: Rationale and design of the STRENGTH trial. *Clin Cardiol* 2018; 41: 1281–1288.
58. Botta M, Audano M, Sahebkar A, et al. PPAR agonists and metabolic syndrome: An established role? *Int J Mol Sci* 2018; 19: ▮▮ [AQ17] [AQ18].
59. Bays HE, Ballantyne CM, Kastelein JJ, et al. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multicenter, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial). *Am J Cardiol* 2011; 108: 682–690.
60. Bays HE, Braeckman RA, Ballantyne CM, et al. Icosapent ethyl, a pure EPA omega-3 fatty acid: effects on lipoprotein particle concentration and size in patients with very high triglyceride levels (the MARINE study). *J Clin Lipidol* 2012; 6: 565–572.
61. Bays HE, Ballantyne CM, Braeckman RA, et al. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: Effects on circulating markers of inflammation from the MARINE and ANCHOR studies. *Am J Cardiovasc Drugs* 2013; 13: 37–46.
62. Bays HE, Ballantyne CM, Braeckman RA, et al. Icosapent ethyl (eicosapentaenoic acid ethyl ester): Effects upon high-sensitivity C-reactive protein and lipid parameters in patients with metabolic syndrome. *Metab Syndr Relat Disord* 2015; 13: 239–247.
63. Ballantyne CM, Braeckman RA, Bays HE, et al. Effects of icosapent ethyl on lipoprotein particle concentration and size in statin-treated patients with persistent high triglycerides (the ANCHOR Study). *J Clin Lipidol* 2015; 9: 377–383.
64. Braeckman RA, Manku MS, Bays HE, et al. Icosapent ethyl, a pure EPA omega-3 fatty acid: effects on plasma and red blood cell fatty acids in patients with very high triglyceride levels (results from the MARINE study). *Prostaglandins Leukot Essent Fatty Acids* 2013; 89: 195–201.
65. Bays HE, Ballantyne CM, Doyle RT Jr, et al. Icosapent ethyl: Eicosapentaenoic acid concentration and triglyceride-lowering effects across clinical studies. *Prostaglandins Other Lipid Mediat* 2016; 125: 57–64.
66. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. Epub ahead of print 13 November 2018. DOI: 10.1056/NEJMoa1812792. [AQ19].
67. Bhatt DL, Steg G and Effects of icosapent ethyl on total ischemic events: From REDUCE-IT. *J Am Coll Cardiol* 2019. DOI: 10.1016/j.jacc.2019.02.032. [AQ20].
68. Bhatt DL. Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial – REDUCE-IT. American College of Cardiology Annual Scientific Session (ACC 2019), New Orleans, Louisiana, USA, 18 March 2019. [AQ21].
69. Toth PP, Granowitz C, Hull M, et al. High triglycerides are associated with increased cardiovascular events, medical costs, and resource use: A real-world administrative claims analysis of statin-treated patients with high residual cardiovascular risk. *J Am Heart Assoc* 2018; 7: e008740.
70. Hegele RA, Ginsberg HN, Chapman MJ, et al. The polygenic nature of hypertriglyceridaemia: Implications for definition, diagnosis, and management. *Lancet Diabetes Endocrinol* 2014; 2: 655–666.

71. Lan NS, Fegan PG, Yeap BB, et al. Icosapent ethyl for dyslipidaemia in patients with diabetes and coronary artery disease: Act now to reduce it. *Diabetes Obes Metab*. Epub ahead of print 6 March 2019. DOI: 10.1111/dom.13689 [AQ22].
72. Lim GB. Hypertriglyceridaemia – REDUCE-IT with icosapent ethyl. *Nat Rev Cardiol* 2019; 16: 1.
73. Ganda OP, Bhatt DL, Mason RP, et al. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol* 2018; 72: 330–343.
74. Raza-Iqbal S, Tanaka T, Anai M, et al. Transcriptome analysis of K-877 (a novel selective PPARalpha modulator (SPPARMalpha))-regulated genes in primary human hepatocytes and the mouse liver. *J Atheroscler Thromb* 2015; 22: 754–772.
75. Yamamoto Y, Takei K, Arulmozhiraja S, et al. Molecular association model of PPARalpha and its new specific and efficient ligand, pemafibrate: Structural basis for SPPARMalpha. *Biochem Biophys Res Commun* 2018; 499: 239–245.
76. Ferri N, Corsini A, Sirtori C, et al. PPAR-alpha agonists are still on the rise: An update on clinical and experimental findings. *Expert Opin Investig Drugs* 2017; 26: 593–602.
77. Fruchart JC. Pemafibrate (K-877), a novel selective peroxisome proliferator-activated receptor alpha modulator for management of atherogenic dyslipidaemia. *Cardiovasc Diabetol* 2017; 16: 124.
78. Arai H, Yamashita S, Yokote K, et al. Efficacy and safety of K-877, a novel selective peroxisome proliferator-activated receptor alpha modulator (SPPARMalpha), in combination with statin treatment: Two randomised, double-blind, placebo-controlled clinical trials in patients with dyslipidaemia. *Atherosclerosis* 2017; 261: 144–152.
79. Araki E, Yamashita S, Arai H, et al. Effects of pemafibrate, a novel selective PPARalpha modulator, on lipid and glucose metabolism in patients with type 2 diabetes and hypertriglyceridemia: A randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care* 2018; 41: 538–546.
80. Araki E, Yamashita S, Arai H, et al. The efficacy and safety of pemafibrate in patients with type 2 diabetes and elevated triglyceride levels: 52-week data from the PROVIDE Study. *Diabetes Obes Metab*. Epub ahead of print 5 March 2019. DOI: 10.1111/dom.13686. [AQ23].
81. Arai H, Yamashita S, Yokote K, et al. Efficacy and safety of pemafibrate versus fenofibrate in patients with high triglyceride and low HDL cholesterol levels: A multicenter, placebo-controlled, double-blind, randomized trial. *J Atheroscler Thromb* 2018; 25: 521–538.
82. De Lorgeril M, Salen P, Paillard F, et al. Lipid-lowering drugs and homocysteine. *Lancet* 1999; 353: 209–210.
83. Ishibashi S, Yamashita S, Arai H, et al. Effects of K-877, a novel selective PPARalpha modulator (SPPARMalpha), in dyslipidaemic patients: A randomized, double blind, active- and placebo-controlled, phase 2 trial. *Atherosclerosis* 2016; 249: 36–43.
84. Ishibashi S, Arai H, Yokote K, et al. Efficacy and safety of pemafibrate (K-877), a selective peroxisome proliferator-activated receptor alpha modulator, in patients with dyslipidemia: Results from a 24-week, randomized, double blind, active-controlled, phase 3 trial. *J Clin Lipidol* 2018; 12: 173–184.
85. Pradhan AD, Paynter NP, Everett BM, et al. Rationale and design of the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study. *Am Heart J* 2018; 206: 80–93.
86. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017; 38: 2459–2472.
87. Tunon J, Back M, Badimon L, et al. Interplay between hypercholesterolaemia and inflammation in atherosclerosis: Translating experimental targets into clinical practice. *Eur J Prev Cardiol* 2018; 25: 948–955.
88. Varbo A and Nordestgaard BG. Remnant cholesterol and triglyceride-rich lipoproteins in atherosclerosis progression and cardiovascular disease. *Arterioscler Thromb Vasc Biol* 2016; 36: 2133–2135.
89. Sirtori CR. The FIELD study. *Lancet* 2006; 367: 1141–1142; author reply 1142-1143.
90. Elam MB, Ginsberg HN, Lovato LC, et al. Association of fenofibrate therapy with long-term cardiovascular risk in statin-treated patients with type 2 diabetes. *JAMA Cardiol* 2017; 2: 370–380.
91. Scott R, O'Brien R, Fulcher G, et al. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetes Care* 2009; 32: 493–498.
92. Yamashita S, Arai H, Yokote K, et al. Effects of pemafibrate (K-877) on cholesterol efflux capacity and postprandial hyperlipidemia in patients with atherogenic dyslipidemia. *J Clin Lipidol* 2018; 12: 1267–1279 e1264.
93. Bisgaier CL, Oniciu DC and Srivastava RAK. Comparative evaluation of gemcabene and peroxisome proliferator-activated receptor ligands in transcriptional assays of peroxisome proliferator-activated receptors: Implication for the treatment of hyperlipidemia and cardiovascular disease. *J Cardiovasc Pharmacol* 2018; 72: 3–10.
94. Bisgaier CL, Essenburg AD, Barnett BC, et al. A novel compound that elevates high density lipoprotein and activates the peroxisome proliferator activated receptor. *J Lipid Res* 1998; 39: 17–30.
95. Srivastava RAK, Cornicelli JA, Markham B, et al. Gemcabene, a first-in-class lipid-lowering agent in late-stage development, down-regulates acute-phase C-reactive protein via C/EBP-delta-mediated transcriptional mechanism. *Mol Cell Biochem* 2018; 449: 167–183.
96. Oniciu DC, Hashiguchi T, Shibazaki Y, et al. Gemcabene downregulates inflammatory, lipid-altering and cell-signaling genes in the STAM model of NASH. *PLoS One* 2018; 13: e0194568.

97. Diehl AM and Day C. Cause, pathogenesis, and treatment of nonalcoholic steatohepatitis. *N Engl J Med* 2017; 377: 2063–2072.
98. Bays HE, McKenney JM, Dujovne CA, et al. Effectiveness and tolerability of a new lipid-altering agent, gemcabene, in patients with low levels of high-density lipoprotein cholesterol. *Am J Cardiol* 2003; 92: 538–543.
99. Stein E, Bays H, Koren M, et al. Efficacy and safety of gemcabene as add-on to stable statin therapy in hypercholesterolemic patients. *J Clin Lipidol* 2016; 10: 1212–1222.
100. Gemphire. Gemphire to present new COBALT-1 clinical data at the 2017 FH Global Summit 9/25/17, http://ir.gemphire.com/phoenix.zhtml?c=254241&p=irol-newsArticle&ID=2302595 (2017, accessed) [AQ24].
101. Bisgaier CL, Oniciu DC and Williams KJ. An orally administered small molecule that inhibits hepatic sulfatase-2 expression in vivo: A novel strategy to correct diabetic dyslipoproteinemia with implications for residual atheroslcerotic cardiovascular disease (ASCVD) risk. *Circulation* 2017; 136: ▮▮ [AQ25].
102. Bisgaier CL and Auerbach BJ. Gemcabene and atorvastatin alone and combined markedly reduce LDL-C in LDL receptor deficient mice, a model of homozygous familial hypercholesterolemia. *Circulation* 2015; 132: ▮▮.
103. Chen K and Williams KJ. Molecular mediators for raft-dependent endocytosis of syndecan-1, a highly conserved, multifunctional receptor. *J Biol Chem* 2013; 288: 13988–13999.
104. Stanford KI, Bishop JR, Foley EM, et al. Syndecan-1 is the primary heparan sulfate proteoglycan mediating hepatic clearance of triglyceride-rich lipoproteins in mice. *J Clin Invest* 2009; 119: 3236–3245.
105. Corsini A, Bellosta S and Davidson MH. Pharmacokinetic interactions between statins and fibrates. *Am J Cardiol* 2005; 96: 44K–49K; discussion 34K-35K.
106. Armitage J, Holmes MV and Preiss D. Cholesteryl ester transfer protein inhibition for preventing cardiovascular events: JACC review topic of the week. *J Am Coll Cardiol* 2019; 73: ▮▮ [AQ26].
107. Shrestha S, Wu BJ, Guiney L, et al. Cholesteryl ester transfer protein and its inhibitors. *J Lipid Res* 2018; 59: 772–783.
108. Van Capelleveen JC, Kastelein JJ, Zwinderman AH, et al. Effects of the cholesteryl ester transfer protein inhibitor, TA-8995, on cholesterol efflux capacity and high-density lipoprotein particle subclasses. *J Clin Lipidol* 2016; 10: 1137–1144 e1133.
109. Pirillo A and Catapano AL. Increasing high-density lipoprotein cholesterol levels for cardiovascular benefit: The end of a dream? *Eur J Prev Cardiol*. Epub ahead of print 14 December 2018. DOI: 10.1177/2047487318820976 [AQ27].
110. Bowman L, Hopewell JC, et al.; HPS3/TIMI55–REVEAL Collaborative Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med* 2017; 377: 1217–1227.
111. Nissen SE, Pillai SG, Nicholls SJ, et al. ADCY9 genetic variants and cardiovascular outcomes with evacetrapib in patients with high-risk vascular disease: A nested case–control study. *JAMA Cardiol* 2018; 3: 401–408.
112. Hopewell J. Impact of ADCY9 on response to anacetrapib among 20,000 participants in the HPS3/TIMI55-REVEAL Trial. American College of Cardiology 2019 [AQ28].
113. Barnhart JW, Sefranka JA and McIntosh DD. Hypocholesterolemic effect of 4,4'-(isopropylidenedithio)-bis(2,6-di-t-butylphenol) (probucol). *Am J Clin Nutr* 1970; 23: 1229–1233.
114. Buckley MM, Goa KL, Price AH, et al. Probucol. A reappraisal of its pharmacological properties and therapeutic use in hypercholesterolaemia. *Drugs* 1989; 37: 761–800.
115. Feher MD, Webb JC, Patel DD, et al. Cholesterol-lowering drug therapy in a patient with receptor-negative homozygous familial hypercholesterolaemia. *Atherosclerosis* 1993; 103: 171–180.
116. Matsuzawa Y, Yamashita S, Funahashi T, et al. Selective reduction of cholesterol in HDL2 fraction by probucol in familial hypercholesterolemia and hyperHDL2 cholesterolemia with abnormal cholesteryl ester transfer. *Am J Cardiol* 1988; 62: 66B–72B.
117. Franceschini G, Sirtori M, Vaccarino V, et al. Mechanisms of HDL reduction after probucol. Changes in HDL subfractions and increased reverse cholesteryl ester transfer. *Arteriosclerosis* 1989; 9: 462–469.
118. Ishigami M, Yamashita S, Sakai N, et al. High-density lipoproteins from probucol-treated patients have increased capacity to promote cholesterol efflux from mouse peritoneal macrophages loaded with acetylated low-density lipoproteins. *Eur J Clin Invest* 1997; 27: 285–292.
119. Hirano K, Ikegami C, Tsujii K, et al. Probucol enhances the expression of human hepatic scavenger receptor class B type I, possibly through a species-specific mechanism. *Arterioscler Thromb Vasc Biol* 2005; 25: 2422–2427.
120. Takiguchi S, Ayaori M, Yakushiji E, et al. Hepatic overexpression of endothelial lipase lowers high-density lipoprotein but maintains reverse cholesterol transport in mice: Role of scavenger receptor class B Type I/ATP-binding cassette transporter A1-dependent pathways. *Arterioscler Thromb Vasc Biol* 2018; 38: 1454–1467.
121. Yamashita S, Ruscica M, Macchi C, et al. Cholesteryl ester transfer protein: An enigmatic pharmacology – antagonists and agonists. *Atherosclerosis* 2018; 278: 286–298.
122. Walldius G, Erikson U, Olsson AG, et al. The effect of probucol on femoral atherosclerosis: The Probucol Quantitative Regression Swedish Trial (PQRST). *Am J Cardiol* 1994; 74: 875–883.
123. Cote G, Tardif JC, Lesperance J, et al. Effects of probucol on vascular remodeling after coronary angioplasty. Multivitamins and Protocol Study Group. *Circulation* 1999; 99: 30–35.

124. Tardif JC, Cote G, Lesperance J, et al. Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. Multivitamins and Probucol Study Group. *N Engl J Med* 1997; 337: 365–372.
125. Sawayama Y, Shimizu C, Maeda N, et al. Effects of probucol and pravastatin on common carotid atherosclerosis in patients with asymptomatic hypercholesterolemia. Fukuoka Atherosclerosis Trial (FAST). *J Am Coll Cardiol* 2002; 39: 610–616.
126. Yamashita S, Hbujo H, Arai H, et al. Long-term probucol treatment prevents secondary cardiovascular events: A cohort study of patients with heterozygous familial hypercholesterolemia in Japan. *J Atheroscler Thromb* 2008; 15: 292–303.
127. Kasai T, Miyauchi K, Kubota N, et al. Probucol therapy improves long-term (>10-year) survival after complete revascularization: A propensity analysis. *Atherosclerosis* 2012; 220: 463–469.
128. Kim BJ, Lee EJ, Kwon SU, et al. Prevention of cardiovascular events in Asian patients with ischaemic stroke at high risk of cerebral haemorrhage (PICASSO): A multicentre, randomised controlled trial. *Lancet Neurol* 2018; 17: 509–518.
129. Dussault S, Dhahri W, Desjarlais M, et al. Elsibucol inhibits atherosclerosis following arterial injury: Multifunctional effects on cholesterol levels, oxidative stress and inflammation. *Atherosclerosis* 2014; 237: 194–199.
130. Tardif JC, Gregoire J, Schwartz L, et al. Effects of AGI-1067 and probucol after percutaneous coronary interventions. *Circulation* 2003; 107: 552–558.
131. Tardif JC, Gregoire J, L'Allier PL, et al. Effects of the antioxidant succinobucol (AGI-1067) on human atherosclerosis in a randomized clinical trial. *Atherosclerosis* 2008; 197: 480–486.
132. Tardif JC, McMurray JJ, Klug E, et al. Effects of succinobucol (AGI-1067) after an acute coronary syndrome: A randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 371: 1761–1768.
133. Rohatgi A, Khera A, Berry JD, et al. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med* 2014; 371: 2383–2393.
134. Yamashita S, Masuda D, Ohama T, et al. Rationale and design of the PROSPECTIVE trial: Probucol trial for secondary prevention of atherosclerotic events in patients with prior coronary heart disease. *J Atheroscler Thromb* 2016; 23: 746–756.
135. Ho PM, Spertus JA, Masoudi FA, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. *Arch Intern Med* 2006; 166: 1842–1847.
136. Koopal C, Visseren FLJ, Westerink J, et al. Predicting the effect of fenofibrate on cardiovascular risk for individual patients with type 2 diabetes. *Diabetes Care* 2018; 41: 1244–1250.
137. Khera AV, Cuchel M, de la Llera-Moya M, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med* 2011; 364: 127–135.
138. Du L, Cheng Z, Zhang Y, et al. The impact of medication adherence on clinical outcomes of coronary artery disease: A meta-analysis. *Eur J Prev Cardiol* 2017; 24: 962–970.
139. Santos RD. Inadequate control of atherosclerotic cardiovascular disease risk factors in Europe: EUROASPIRE repeats itself. *Eur J Prev Cardiol*. Epub ahead of print 21 February 2019. DOI: 10.1177/2047487319831476 **[AQ29]**.
140. Philip S, Chowdhury S, Nelson JR, et al. A novel cost-effectiveness model of prescription eicosapentaenoic acid extrapolated to secondary prevention of cardiovascular diseases in the United States. *J Med Econ* 2016; 19: 1003–1010.
141. European Medicine Agency. List of nationally authorised medicinal products – pitavastatin. 2019.
142. European Medicine Agency. Omega-3 fatty acid medicines no longer considered effective in preventing heart disease. 2018 **[AQ30]**.
143. Blair HA. Pemafibrate: First global approval. *Drugs* 2017; 77: 1805–1810.
144. Kodera S, Morita H, Kiyosue A, et al. Cost-effectiveness of statin plus eicosapentaenoic acid combination therapy for cardiovascular disease prevention in Japanese patients with hypercholesterolemia – an analysis based on the Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS). *Circ J* 2018; 82: 1076–1082.
145. Ruscica M, Watts GF and Sirtori CR. PCSK9 in HIV infection: New opportunity or red herring? *Atherosclerosis*. Epub ahead of print 2 March 2019. DOI: 10.1016/j.atherosclerosis.2019.03.002 **[AQ31]**.
146. Hegele RA and Tsimikas S. Lipid-lowering agents. *Circ Res* 2019; 124: 386–404.