Review Article

Treatment of Hypertriglyceridemia: A Review of Therapies in the Pipeline

Journal of Pharmacy Practice
2023, Vol. 36(3) 650–661

DOI: 10.1177/08971900211053489
journals.sagepub.com/home/jpp
SAGE

Jiashan Xu, PharmD[1,2] and Emily Ashjian, BCPS, BCACP, CDCES[2,3]

Abstract

Background: The 2018 American College of Cardiology/American Heart Association (ACC/AHA) guidelines and 2021 ACC Expert Consensus Decision Pathway recommend nonpharmacological interventions and initiation of statin therapy for patients with moderate hypertriglyceridemia and addition of fibrates or omega-3 fatty acids in severe hypertriglyceridemia. Although the association between triglyceride (TG) lowering and atherosclerotic cardiovascular disease (ASCVD) risk reduction remains controversial, patients with hypertriglyceridemia may represent a subgroup that require additional therapy to further reduce residual ASCVD risk. Moreover, medications that target novel pathways could provide alternative options for patients who are intolerant of existing therapies or doses needed to provide adequate triglyceride lowering. **Objective:** Assess recent evidence for TG-lowering agents including omega-3 fatty acid-based therapies, PPARα modulators, apoC-III mRNA antisense inhibitors, angiopoietin-like 3 (ANGPTL3) antibodies, and herbal supplements. **Methods:** A literature search was performed using PubMed with *hypertriglyceridemia* specified as a MeSH term or included in the title or abstract of the article along with each individual agent. For inclusion, trials needed to have a primary or secondary outcome of TG levels or TG lowering. **Conclusion:** Currently, the only US Food and Drug Administration approved medication for CV risk reduction in patients with hypertriglyceridemia is icosapent ethyl. Results from phase 3 trials for CaPre, pemafibrate, and volanesorsen as well as additional evidence for pipeline pharmacotherapies with novel mechanisms of action (e.g., ApoC-III mRNA antisense inhibitors and ANGPTL3 antibodies) will help to guide future pharmacotherapy considerations for patients with hypertriglyceridemia.

Keywords

hypertriglyceridemia, omega-3 fatty acids, pemafibrate, pharmacotherapy

Introduction

Elevated cholesterol is a known risk factor for the development of atherosclerotic cardiovascular disease (ASCVD). Therapeutic modalities focus on lifestyle changes and incorporation of lipid-lowering medications.[1-4] Low-density lipoprotein cholesterol (LDL-C) is the dominant form of atherogenic cholesterol. Statins, also known as hydroxymethylglutaryl-CoA reductase inhibitors, are the current cornerstone of therapy for reducing LDL-C, with clear evidence for reducing risk of ASCVD events.[1,3] However, elevated triglyceride (TG) levels are also associated with the development of cardiovascular disease (CVD).[1,3-9]

Hypertriglyceridemia is a common abnormality seen in clinical practice. Between 2013 and 2016, approximately 22.2% of US adults had high TG levels.[2] The 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients with Persistent Hypertriglyceridemia defines mild to moderate hypertriglyceridemia as fasting TG ≥150 mg/dL or nonfasting TG ≥ 175 mg/dL and severe hypertriglyceridemia as fasting TG ≥ 500 mg/dL and especially ≥ 1000 mg/dL.[10] In moderate hypertriglyceridemia, excess TG are carried in the circulation by increased very-low-density lipoprotein cholesterol (VLDL-C), which is also believed to be atherogenic. In severe hypertriglyceridemia, levels of VLDL-C and chylomicrons increase, which raises the risk of acute pancreatitis.[1,4] Severe hypertriglyceridemia may account for up to 10% of pancreatitis episodes with higher incidence seen at higher TG levels.[11] Although the exact pathophysiology remains unclear, the most commonly accepted mechanism suggests the breakdown of TG via

[1]Department of Pharmacy, Michigan Medicine, Ann Arbor, MI, USA
[2]University of Michigan College of Pharmacy, Ann Arbor, MI, USA
[3]Michigan Medicine, Ann Arbor, MI, USA

Corresponding Author:
Jiashan Xu, Department of Pharmacy, Michigan Medicine, 1111 E. Catherine St, Ann Arbor, MI 48109, USA.
Email: jiashan.x@gmail.com

pancreatic lipases into free fatty acids (FFA) in high concentrations is harmful due to FFA aggregation which leads to injury of the pancreatic acinar cells and capillaries.[4,12-14] The 2 main goals of treatment of hypertriglyceridemia are to prevent CVD and pancreatitis.

Hypertriglyceridemia may be categorized as acquired or genetic. Acquired hypertriglyceridemia may be secondary to poorly controlled diabetes mellitus, insulin resistance, obesity, alcohol abuse, chronic kidney disease, hypothyroidism, or pregnancy (particularly in the third trimester).[3,4,10,14] Additionally, medications such as atypical antipsychotics (clozapine, olanzapine, risperidone), oral estrogens (contraception, postmenopausal replacement), tamoxifen, raloxifene, antiretroviral protease inhibitors, systemic corticosteroids, immunosuppressive drugs (cyclosporine, sirolimus, tacrolimus), α-interferon, and bile acid sequestrants may increase TG.[1,4,10,14] Genetic disorders that result in elevated TG levels, such as familial chylomicronemia syndrome (FCS) and familial apolipoprotein C-II (apoC-II) deficiency, may arise from altered function of lipoprotein lipase (LPL), apoC-II, apolipoprotein AV, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), or mutations in other enzymes that result in decreased clearance or increased production of TG-rich lipoproteins.[3,4,14]

As previously mentioned, residual ASCVD risk may be due to elevations in TG despite adequate LDL-C lowering.[5-9] In the Treating to New Targets (TNT) study, patients with a history of ASCVD and LDL-C < 130 mg/dL on atorvastatin 80 mg daily had a 22% relative risk reduction of major adverse cardiovascular events (MACE). Although LDL-C decreased to a mean of 77 mg/dL, a residual 8.7% risk remained.[15] Subsequently, a pooled analysis of the TNT and Incremental Decrease in Endpoints Through Aggressive Lipid-lowering trials showed increasing risk of cardiovascular events with increasing TG levels in statin-treated patients at recommended LDL-C goals. The authors also noted a 33% higher risk for a cardiovascular event in patients with TG > 150 mg/dL compared to those with TG < 150 mg/dL.[16] Additionally, a study using Mendelian randomization analysis included over 650 000 participants and compared genes associated with TG and LDL-C lowering with risk of coronary heart disease (CHD) (coronary death, myocardial infarction (MI), or coronary revascularization). Despite differences in individual lipid levels, carriers of gene variants associated with lower TG and carriers of gene variants associated with lower LDL-C had similar risk of CHD that were independent and proportional to the absolute change in apolipoprotein B (apoB).[17] ApoB is a protein that provides structural integrity for atherogenic lipoproteins including LDL-C, VLDL-C, and chylomicrons.[18] A 5-fold reduction in TG (approximately 200 mg/dL) would be required to achieve the same cardiovascular risk reduction as lowering LDL-C by 40 mg/dL based on attainment of an equivalent apoB reduction.[17] Although the association between TG lowering and ASCVD risk reduction remains controversial due to the confounding role of additional cholesterol markers such as high-density lipoprotein cholesterol (HDL-C), VLDL-C, and apoB, patients with hypertriglyceridemia may represent a subgroup that require additional therapy to further reduce residual ASCVD risk.[16] Moreover, medications that target novel pathways could provide alternative options for patients who are intolerant of existing therapies or doses needed to provide adequate triglyceride lowering.

The 2018 ACC/AHA guidelines and the 2021 ACC Expert Consensus Decision Pathway recommend nonpharmacological interventions including weight loss, physical activity, and avoidance of dietary fats and alcohol as well as addressing secondary factors such as optimization of diabetes control for adults ≥ 20 years of age with moderate hypertriglyceridemia. After lifestyle and secondary factors are addressed, initiation or intensification of statin therapy may be considered for patients 40-75 years of age with moderate or severe hypertriglyceridemia and a 10-year ASCVD risk ≥ 7.5% with the goal of reducing ASCVD risk. For patients with severe hypertriglyceridemia, addition of fibrates or omega-3 fatty acids (O3FA) is reasonable to prevent acute pancreatitis.[1,10] See Table 1 for current US Food and Drug Administration (FDA) approved therapies for the treatment of hypertriglyceridemia. In this review, we aim to assess evidence for effective TG-lowering agents recently approved or still in the pipeline including O3FA-based therapies, PPARα modulators, apoC-III mRNA antisense inhibitors, angiopoietin-like 3 (ANGPTL3) antibodies, and herbal supplements.

Methods

An initial search for pharmacotherapies using Cochrane Library (*hypertriglyceridemia treatment* included in the title or abstract or as a keyword) and PubMed (*hypertriglyceridemia* [specified as a MeSH term or included in the title or abstract of the article] and *therapeutics* or *treatments*) identified the following agents: Vascepa, eicosapentaenoic acid (EPA), or icosapent ethyl; omega-3-carboxylic acids or Epanova; CaPre or AMR101; epeleuton or DS102; pemafibrate or K-877; volanesorsen, ISIS-APOCIIIRx or ISIS 304801; AKCEA-APOCIII-LRx; evinacumab or REGN1500; vupanorsen, IONIS-ANGPTL3-LRx, AKCEA-ANGPTL3-LRx, or ISIS 703802; ARO-ANG3; and xuezhitong or XZT. Subsequently, a literature search was performed from August 2020 to May 2021 using PubMed with *hypertriglyceridemia* specified as a MeSH term or included in the title or abstract along with each individual agent.

The literature search was not restricted by geography or publication date, but only full-text articles published in English were included. Titles and abstracts were screened to determine inclusion or exclusion. To be included, trials needed to have a primary or secondary outcome of TG levels or TG lowering. Trials were excluded for the following reasons: the medication was no longer available on the market, no trials were conducted in patients with hypertriglyceridemia, more

Table 1. FDA Approved Non-Statin Therapies for Hypertriglyceridemia.[1,14,40-43,93]

Pharmacologic Category	Medication	Dose Range	Monitoring Parameters or Possible SE
Fibrates	Fenofibrate	40 to 160 mg/day[a]	•Rhabdomyolysis, higher risk with gemfibrozil, and statin combination
	Gemfibrozil	600 mg twice daily	•Monitor liver function tests and periodic blood counts during first year of therapy
Omega-3 fatty acids	Omega-3 ethyl esters	4 g/day	•Fishy aftertaste •GI upset
	Icosapent ethyl	2 g twice daily with meals	•Bleeding, risk may be increased with concomitant anticoagulant/ antiplatelet use •Constipation •Musculoskeletal pain •Atrial fibrillation

Abbreviations: GI, gastrointestinal; SE, side effects.
[a]Dose varies based on the formulation.

than 5 years had elapsed since the last trial results were published, or further development for use in patients with hypertriglyceridemia had been abandoned.

The literature review was supplemented by review of expert recommendation reports or opinions, examination of references from included studies, an individual search on ClinicalTrials.gov for each identified medication, and inclusion of information from package inserts, new drug applications (NDA), or manufacturer press releases.

Pharmacotherapy

Omega-3 Fatty Acid-Based Therapies. O3FA include eicosapentaenoic acid and docosahexaenoic acid (DHA). The most common dietary source of EPA and DHA is fatty fish such as tuna, salmon, mackerel, and herring.[10,19] The mechanism of O3FA has not been fully elucidated but is likely multifactorial including reduced hepatic secretion of TG-rich lipoproteins and inhibition of diacylglycerol acyltransferase, the major enzyme that catalyzes the formation of TGs in the liver.[20,21]

Prescription omega-3 ethyl esters (e.g., Lovaza, Omarcor, Omtryg) contain a mixture of EPA and DHA. At the FDA approved dose of 4 g/day, it is generally well-tolerated and efficacious with ≥ 30% TG lowering in patents with TG ≥ 500 mg/dL.[14] Use of O3FA (0.5 g/day to 5 g/day) for primary and secondary prevention was evaluated in a 2020 Cochrane systematic review that combined 86 randomized control trials with 162 796 participants. The authors concluded EPA and DHA had little or no effect on all-cause mortality, cardiovascular mortality, or cardiovascular events.[22]

Icosapent ethyl (Vascepa), an ethyl ester formulation of EPA, produced positive results in its cardiovascular outcomes trial. Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial (REDUCE-IT) included 8179 high-risk patients on stable statin therapy. Patients were ≥ 45 years of age with CVD (history of coronary artery disease, cerebrovascular or carotid disease, or peripheral arterial disease) (e.g., secondary prevention) or ≥ 50 years of age with diabetes and at least 1 risk factor (e.g., primary prevention). For the primary composite endpoint of MACE (cardiovascular death, MI, stroke, coronary revascularization, and unstable angina requiring hospitalization), icosapent ethyl 2 g twice daily resulted in a statistically significant 25% relative risk reduction compared to mineral oil placebo (17.2% vs 22%). Furthermore, each of the individual components of MACE was statistically significant for decreased events with icosapent ethyl including ≥ 20% reduction in cardiovascular death. The authors postulated that EPA-based O3FA do not raise LDL-C while DHA-based formulations do. Median percent increase in LDL-C was 3.1% with icosapent ethyl compared to 10.2% with placebo ($P < .001$). However, 71% of patients were included as part of the secondary prevention cohort but only 30% were on high intensity statin therapy.[23] As the primary prevention cohort subgroup analysis was not statistically significant, it is uncertain if the cardiovascular benefit applies to this patient population. Additionally, it is unclear if statin therapy was optimized for all patients in the trial. Icosapent ethyl was the first FDA approved medication for cardiovascular risk reduction as an add-on to maximally tolerated statin therapy for patients with TG ≥ 150 mg/dL and either established CVD or type 2 diabetes mellitus (T2DM) with 2 or more risk factors.[14,24]

Another O3FA-based therapy, omega-3-carboxylic acid (Epanova), is formulated as a FFA to increase bioavailability without the need to administer with food. Initial FDA approval was granted for severe hypertriglyceridemia based on results from **E**pano**V**a f**O**r **L**owering **V**ery high triglycerid**E**s (EVOLVE), where 399 patients with TG ≥ 500 mg/dL were randomized to omega-3-carboxylic acid 2 g/day, 3 g/day, or 4 g/day or placebo olive oil.[25,26] Omega-3-carboxylic acid produced a statistically significant 25-31% TG reduction compared to 4.3% with placebo.[25] Subsequently, to evaluate cardiovascular outcomes, **ST**atin **R**esidual risk reduction with **E**pa**N**ova in hi**G**h CV risk patien**T**s with **H**ypertriglyceridemia (STRENGTH) randomized 13 078 statin-treated adults with or at high risk for CVD to omega-3-carboxylic acid 4 g/day or placebo corn oil. Similar to REDUCE-IT, both primary and

secondary prevention were evaluated with a primary composite outcome of MACE (cardiovascular death, MI, stroke, coronary revascularization, or unstable angina requiring hospitalization).[27] However, the trial was discontinued in January 2020 due to low likelihood of demonstrating cardiovascular benefit as MACE occurred in 12% of the omega-3-carboxylic acid group vs 12.2% in the placebo group (P = .84) despite 19% TG reduction from baseline. The authors noted the lack of benefit may be due to administration of DHA rather than solely EPA and a higher percentage of patients without established CVD at baseline.[28] See Table 2 for a summary of pipeline pharmacotherapies.

Similar to omega-3-carboxylic acid, a krill oil-based formulation containing DHA and EPA (CaPre) is formulated to increase absorption regardless of food intake. Initial phase 2 trials **TRI**al **F**or **E**fficacy of **C**apre on hypertriglyceridemi**A** (TRIFECTA) and Multicenter **C**aPre **O**pen **L**abel Randomized Dose-Ranging Phase II **T**rial to Assess Efficacy/Safety in Patients with Mild-to-High Hypertriglyceridemia (COLT) included 387 and 288 participants, respectively. Approximately 90% had mild to moderate hypertriglyceridemia (200-499 mg/dL), 10% had severe hypertriglyceridemia, and 30% were on statin therapy.[29-31] Results noted a statistically significant absolute TG reduction of 9.1% with 1 g/day, 9.7% with 2 g/day, and 14.4% with 4 g/day.[31] Subsequently, 2 parallel phase 3 trials, A Phase 3 S**T**udy of Ca**P****R**e **I**n **LO**wering Very hi**G**h Trigl**Y**cerides (TRILOGY 1 and TRILOGY 2) compared CaPre 4 g/day to placebo for effectiveness in TG reduction in severe hypertriglyceridemia.[32,33] In January 2020, topline results for TRILOGY 1 were released noting a 30.5% TG reduction compared to 27.5% in the placebo group.[34] This did not reach statistical significance due to an unusually large placebo effect that was later attributed to 5 out of 54 sites that disproportionately contributed to the placebo response as well as potential protocol violations.[35] TRILOGY 2 topline results were released in August 2020 and showed a similar TG reduction (30.4%) in the CaPre group with a smaller placebo response (17.9%) compared to TRILOGY 1, but results did not reach statistical significance (P = .19). As such, the manufacturer did not file for an NDA but they will complete the full data analyses including secondary and exploratory endpoints as well as combine data from TRIOLOGY 1 and 2.[36]

A novel second generation synthetic O3FA currently in phase 3 trials is epeleuton, a 15-hydroxy EPA ethyl ester derived from a downstream metabolite of EPA.[37] The first phase 2 trial was conducted in nonalcoholic fatty liver disease (NAFLD) with randomization to epeleuton 500 mg twice daily, 1000 mg twice daily, or placebo light liquid paraffin twice daily.[38] Post-hoc analysis noted epeleuton 1000 mg twice daily reduced TG by 13.9% while TG increased in the placebo group by 24.1% (P = .0001).[37] As subgroup analysis in patients with HbA1c > 6.5% noted an A1c reduction of 1.1% (P = .047), a second phase 2 trial was initiated in adults with hypertriglyceridemia (TG 200-750 mg/dL) and T2DM (HbA1c 7.5-9.5%). **TRI**gyceride **A**nd **G**lucose Control with **E**peleuton in Metabolic Syndrome Patients (TRIAGE) will assess efficacy in lowering TG and HbA1c from baseline with estimated completion in December 2021.[37,39] Results from TRIAGE will determine whether or not the manufacturer pursues a phase 3 trial.

To summarize, icosapent ethyl is currently the only O3FA-based therapy with results indicative of cardiovascular benefit and FDA approval for cardiovascular risk reduction. However, generalizability of these results is limited by patient characteristics within REDUCE-IT. Omega-3-ethyl esters and

Table 2. Summary of Pipeline Triglyceride Lowering Pharmacotherapies.

Pharmacologic category	Medication	Phase	Current trial status
Omega-3 fatty acids	Omega-3-carboxylic acids[28]	3	STRENGTH: discontinued in Jan 2020 due to low likelihood of demonstrating cardiovascular benefit
	CaPre[34-36]	3	Awaiting publication of full analysis from TRILOGY 1 and 2; topline data did not reach statistical significance due to unusually large placebo effect
	Epeleuton[37,39]	2b	TRIAGE: estimated completion in Dec 2021
Selective PPARα Modulators	Pemafibrate[53,54]	3	PROMINENT: estimated completion in May 2022
Apolipoprotein C-III (ApoC-III) mRNA antisense inhibitors	Volanesorsen[64,65]	3	COMPASS: adverse effect profile may preclude use
	AKCEA-APOCIII-LRx[66,69-71]	2	Completed in patients with hypertriglyceridemia
		3	BALANCE initiated in patients with FCS; estimated completion in Jun 2023
	ARO-APOC3[75]	2b	Estimated completion in Jul 2022
Angiopoietin-like 3 (ANGPTL3) antibodies	Evinacumab[81]	2	Study completed in Jul 2020 but results not yet published
	Vupanorsen[85]	2b	TRANSLATE-TIMI 70: estimated completion in Jan 2022
	ARO-ANG3[88]	2b	IND filed to initiate study in patients with mixed dyslipidemia

Abbreviations: FCS, familial chylomicronemia syndrome; IND, investigational new drug application; PPARα, peroxisome proliferator-activated receptor alpha; PROMINENT, Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes; STRENGTH, STatin Residual risk reduction with EpaNova in hiGh CV risk patienTs with Hypertriglyceridemia; TRANSLATE-TIMI 70, TaRgeting ANGPTL3 with an aNtiSense oLigonucleotide in AdulTs with dyslipidemia; TRIAGE, TRIglyceride And Glucose Control With Epeleuton in Metabolic Syndrome Patients; TRILOGY, A Phase 3 STudy of CaPRe In LOwering Very hiGh TriglYcerides.

omega-3-carboxylic acids do not have data supporting their use for cardiovascular risk reduction. For pipeline therapies, full data analyses from TRILOGY 1 and 2 for CaPre and TRIAGE for epeleuton are not yet available.

Selective PPARα Modulators (PPARMα). In addition to O3FA, peroxisome proliferator-activated receptor alpha (PPARα) agonists, also known as fibrates, are guideline recommended for severe hypertriglyceridemia.[1,10] PPAR is part of a family of nuclear receptors and includes isotypes PPARα, PPARβ/δ, and PPARγ. Activation of PPARα results in upregulation of the synthesis of apolipoprotein A-I, fatty acid transport protein, and LPL, resulting in increased VLDL-C clearance and elimination of TG-rich particles. However, limitations of fibrates include increased risk of myopathy and rhabdomyolysis due to drug-drug interactions between gemfibrozil and statins, transient elevations in serum creatinine with fenofibrate, and liver enzyme elevations.[40-43] These limitations prompted a search for selective PPARMα modulators with improved potency and reduced side effects.[44] Structurally, the benzoxazole and phenoxyalkyl side-chains of pemafibrate create a Y-configuration with improved fit within the binding pocket, resulting in increased PPARα potency and selectivity compared to fenofibrate.[44,45] Additionally, transcriptome analysis shows pemafibrate upregulates genes that encode mannose-binding lectin 2 (*MBL2*, involved in innate immune system regulation and inflammation), glutamyl aminopeptidase (*ENPEP*, involved in blood pressure regulation), and fibroblast growth factor 21 (*FGF21*, involved in glucose homeostasis).[44,46]

Numerous trials have validated the efficacy of pemafibrate for lowering TG, both as monotherapy compared to fenofibrate and as add-on to baseline statin therapy (Table 3). Initial phase 2 and 3 trials in adult Japanese patients with dyslipidemia (TG ≥ 150 or 200 mg/dL and HDL-C < 50 mg/dL if male or < 55 mg/dL if female) excluded patients on statin therapy. The authors noted a statistically significantly greater decrease in TG from baseline in the pemafibrate group, ranging from 30.9% to 46.2%, compared to fenofibrate 100 mg daily or 106.6 mg daily (bioequivalent to 124 mg micronized fenofibrate) or placebo.[47,48] One trial demonstrated non-inferiority of pemfibrate 0.1 mg twice daily and 0.2 mg twice daily compared to fenofibrate 200 mg daily as well as superiority of pemafibrate at all doses (0.05 mg, 0.1 mg, and 0.2 mg twice daily) to fenofibrate 100 mg daily for reducing TG.[49]

Two phase 3 trials evaluated pemafibrate as an add-on therapy for residual hypertriglyceridemia in patients on statin

Table 3: Pemafibrate Trials.

Reference	Phase	N	Study population	Statin therapy, %	Duration (weeks)	Intervention	ΔTG
Ishibashi et al. [47]	2	224	• 20-74 y/o • TG ≥ 200 mg/dL • HDL < 50 mg/dL (M) or 55 mg/dL (F)	0	12	• Pemafibrate 0.025, 0.05, 0.1, 0.2 mg BID • Fenofibrate 100 mg/day • Placebo	−30.9% to −42.7% −29.7% +28.5%
Ishibashi et al. [48]	3	225	• > 20 y/o • TG ≥ 150-500 mg/dL • HDL < 50 mg/dL (M) or 55 mg/dL (F)	0	24	• Pemafibrate 0.1 or 0.2 mg BID • Fenofibrate 106.6 mg/day	−45.9% to −46.2% −39.7%
Arai et al. [49]	3	526	• 20-74 y/o • TG 200-1000 mg/dL • HDL < 50 mg/dL (M) or 55 mg/dL (F)	0	12	• Pemafibrate 0.05, 0.1, 0.2 mg BID • Fenofibrate 100, 200 mg/day • Placebo	−46.3% to −51.8% −38.3% to −51.5% −2.7%
Arai et al. [50]	3	188	• > 20 y/o • TG ≥ 200 mg/dL • Non-HDL ≥ 150 mg/dL • Pitavastatin	100	12	• Pemafibrate 0.1, 0.2, or 0.4 mg/day • Placebo (e.g., statin monotherapy)	−46.1% to −53.4% −6.9%
	3	423	• > 20 y/o • TG ≥ 200 mg/dL • Any statin		24	• Pemafibrate 0.2 mg/day (fixed dose) OR 0.2 mg -> 0.4 mg (up-titration) • Placebo (e.g., statin monotherapy)	−46.8% to −50.8% −0.8%
Araki et al. [51]	3	166	• > 20 y/o • DM (A1c 6.2-8.0%) • TG 150-100 mg/dL	39.2	24	• Pemafibrate 0.1, 0.2 mg BID • Placebo	−44.3% to −45.1% −10.8%
Araki et al. [52]					52	• Pemafibrate 0.1, 0.2 mg BID • Placebo switched to pemafibrate 0.1 mg BID	−42.3% to −46.4% −48.2%

therapy. One trial included patients on pitavastatin while the other allowed any statin. While no information was provided regarding statin intensity, pemafibrate continued to show approximately 50% TG reduction from baseline.[50] Furthermore, in patients with T2DM and elevated TG, pemafibrate reduced TG by 44-46% from baseline after 24 weeks, and this effect was sustained after 52 weeks ($P < .001$). 39.2% of patients were on statin therapy (atorvastatin 23.1%, pitavastatin 27.7%, rosuvastatin 35.4%, other statins 13.8%).[51,52]

Ongoing, the **P**emafibrate to **R**educe Cardiovascular **O**utco**M**es by Reducing Triglycerides **IN** pati**EN**ts with diabe**T**es (PROMINENT) trial will compare cardiovascular outcomes of pemafibrate 0.2 mg twice daily to placebo in over 10 000 adults with T2DM, high cardiovascular risk, TG 200-499 mg/dL, and on moderate to high intensity statin therapy at baseline. Similar to REDUCE-IT and STRENGTH, patients will be divided into 2 cohorts: (1) established systemic atherosclerosis and (2) primary prevention (high risk defined as age ≥ 50 years if male or ≥ 55 years if female). The primary endpoint is the time to first occurrence of a composite of MI, ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization, and CV death.[53,54]

In Japan, pemafibrate was approved for the treatment of hyperlipidemia under the brand name, Parmodia, in June 2017 at a starting dose of 0.1 mg twice daily to a maximum of 0.2 mg twice daily.[3,55,56] Data submitted by the manufacturers noted pemafibrate is a substrate of several cytochromes including CYP2C8, CYP2C9, CYP3A4, and CYP3A7, and coadministration with cyclosporine or rifampicin is contraindicated. Caution should be used when administered with CYP3A4 inhibitors (e.g., clarithromycin and ritonavir), CYP3A4 inducers (e.g., anticonvulsants, St John's Wort), cholestyramine, and clopidogrel.[56]

Overall, pemafibrate may be a promising agent for the management of hypertriglyceridemia and cardiovascular risk reduction after achievement of LDL-C goals. Results of the PROMINENT trial will guide considerations for future place in therapy.

Apolipoprotein C-III (ApoC-III) mRNA Antisense Inhibitors. Apolipoprotein C-III is a 79 amino acid glycoprotein synthesized primarily in the liver and secondarily in the intestines. Through inhibition of LPL activation, apoC-III inhibits lipolysis of TG-rich lipoproteins.[57] Additionally, apoC-III may have intrinsic atherogenic effects including augmenting inflammatory mediator production and enhancement of LDL-C accumulation in the arterial wall.[58] In a cross-sectional study of over 1400 patients with T2DM without CVD, increased apoC-III levels were associated with coronary artery calcification, a measure of subclinical atherosclerosis.[59] As such, novel antisense oligonucleotides are being developed to inhibit production of apoC-III with the goal of reducing cardiovascular risk.

Volanesorsen (formerly known as ISIS-APOCIIIRx and ISIS-304801) is an antisense oligonucleotide inhibitor of apoC-III mRNA. In the phase 3 APPROACH trial, volanesorsen was studied in 66 patients with FCS. Volanesorsen 300 mg subcutaneously weekly resulted in a 77% TG reduction compared to an 18% increase in the placebo group at month 3 ($P < .001$).[60] However, in August 2018, the FDA rejected approval for use in FCS due to concerns for serious bleeding and thrombocytopenia.[61] APPROACH noted 5 discontinuations due to decline in platelet count. Seventy-six percent (25/33) of patients who received volanesorsen had a confirmed nadir platelet count below the normal level of 140 000/μL compared to 24% (8/33) in the placebo group.[60] In 2019, the European Medicines Agency granted conditional marketing authorization for use in FCS under the brand name Waylivra.[62] Within the European product information, volanesorsen is contraindicated in patients with chronic or unexplained thrombocytopenia and includes warnings for risk factors for developing thrombocytopenia (e.g., body weight < 70 kg or use of antiplatelets, non-steroidal anti-inflammatory drugs, or anticoagulants).[63]

Safety and efficacy of volanesorsen was subsequently evaluated in the COMPASS trial.[64] In 113 patients with severe hypertriglyceridemia, similar TG reductions were seen with 71% reduction from baseline in the volanesorsen group compared to 0.9% reduction in the placebo group at month 3 ($P < .0001$). Trial results also noted decreased incidence of acute pancreatitis as no events occurred in the volanesorsen group while 5 events occurred in 3 patients in the placebo group. The most common adverse events were related to injection-site reactions (91% in the volanesorsen group and 13% in the placebo group) leading to 9 discontinuations in the volanesorsen group.[65]

Due to the platelet reductions in APPROACH, a protocol amendment was implemented for COMPASS in May 2016 where volanesorsen was adjusted from 300 mg weekly to 300 mg every 2 weeks after 13 weeks of treatment in all patients except those who had completed at least 5 months of treatment. During the trial, 5% (2/38) of the placebo group and 13% (10/75) of the volanesorsen group had thrombocytopenia. One patient in the volanesorsen group had a platelet count of < 50,000/μL[65] Mechanisms underlying the decline in platelets remain unclear.[60] The authors concluded that while volanesorsen effectively reduced TG levels, its adverse effect profile may preclude its use.[65]

Another agent targeting apoC-III, AKCEA-APOCIII-LRx, is undergoing phase 2 trials.[66] Addition of an N-acetyl galactosamine moiety is anticipated to have similar efficacy as traditional antisense oligonucleotides but with decreased adverse effects due to reduced systemic exposure with 20 to 30-fold lower doses.[67] Safety, tolerability, pharmacokinetics, and pharmacodynamics were evaluated for single and multiple doses of AKCEA-APOCIII-LRx in a phase 1/2a study in healthy volunteers.[67,68] In the single dose cohorts (10, 30, 60, 90, or 120 mg), TG reductions ranged from 7.3 to 77.1% 14 days after dosing with the highest reduction with the highest dose. In the multiple dose cohorts (15 or 30 mg weekly for 6 weeks or 60 mg every 4 weeks for 3 months), TG

reduction ranged from 59 to 73% 1 week after the last dose with the highest reduction in the group receiving 30 mg weekly. No deaths, serious adverse events, or treatment-emergent adverse events leading to discontinuation of the treatment were noted.[67]

Subsequently, a phase 2 trial in 114 patients with hypertriglyceridemia (TG 200-500 mg/dL) and established CVD or high risk for CVD was completed in February 2020. The trial evaluated the safety and efficacy of AKCEA-APOCIII-LRx at various doses (10 mg weekly, 10 mg every 4 weeks, 15 mg every 2 weeks, or 50 mg every 4 weeks).[66] Preliminary results noted a favorable safety profile with a statistically significant, dose-dependent TG reduction compared to placebo at all doses. The highest dose (50 mg every 4 weeks) resulted in a 62% TG reduction. Ninety-one percent of patients achieved TG < 150 mg/dL.[69] In December 2020, initiation of the phase 3 BALANCE trial was announced, which will randomize up to 60 patients with FCS to receive AKCEA-APOCIII-LRx subcutaneously every 4 weeks for a total of 53 weeks.[70] BALANCE is estimated to be completed in June 2023.[71]

A third agent in development targeting apoC-III is ARO-APOC3. A phase I trial evaluating safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of ARO-APOC3 in healthy adult volunteers, severe hypertriglyceridemia, and FCS was completed in February 2021.[72] Results presented at the 2020 AHA Scientific Sessions noted a mean TG reduction from 74% to 92% and reductions were maintained for more than 12 weeks after the second dose.[73] In March 2021, an investigational new drug application (IND) was filed to initiate a phase 2b dose-finding study in patients with severe hypertriglyceridemia with the primary outcome of percent change from baseline TG at week 24.[74,75]

ANGPTL3 Antibodies. Angiopoietin-like protein 3 is a 460 amino acid polypeptide that regulates lipid levels by inhibiting LPL and endothelial lipase (EL)-mediated hydrolysis of TG and HDL-C. The N-terminal coiled-coil region affects TG levels by inhibiting LPL, the C-terminal fibrinogen-like domain affects angiogenesis, and the linker region between the N- and C-terminals functions as a cleavage site and has activity for inhibition of LPL and EL.[76] Evaluation of over 20 000 individuals from 9 case-control studies of the MI Genetics Consortium noted that compared to non-carriers, individuals who were heterozygous carriers of loss of function mutations for *ANGPTL3*, demonstrated a 17% TG reduction and 12% LDL-C reduction. This was associated with a 34% reduction in the odds of coronary artery disease.[77] The prominent risk reduction and hypolipidemic profile imparts potential for ANGPTL3 inactivation as a pharmacologic target. Novel agents developed to inhibit ANGPTL3 include evinacumab, vupanorsen, and ARO-ANG3.

Evinacumab is a fully human monoclonal antibody inhibitor of ANGPTL3 initially studied in homozygous familial hypercholesterolemia (HoFH) in the **E**vina**C**umab **LIP**id **S**tudi**E**s (ECLIPSE) trial.[78] HoFH is an inherited autosomal dominant disorder of a defect of either the LDL-C receptor or proteins that regulate LDL-C receptor metabolism resulting in an accumulation of LDL-C and increased cardiovascular risk.[79] ECLIPSE was a double-blind, phase 3 trial that randomized 65 HoFH patients on stable lipid-lowering therapy to either intravenous evinacumab 15 mg/kg every 4 weeks or placebo for 24 weeks. Ninety-four percent of patients were receiving statin therapy at baseline with 77% on a high-intensity statin. The primary outcome of percent change in LDL-C from baseline at week 24 was −47.1% in the evinacumab group compared to +1.9% in the placebo group ($P <$ .001). Adverse events were similar between groups; nasopharyngitis, influenza-like illness, dizziness, rhinorrhea, and nausea were more prevalent in the evinacumab group.[78] In February 2021, the FDA approved evinacumab (Evkeeza) as an adjunct to other LDL-C lowering therapies to treat HoFH in patients at least 12 years of age.[80] Other outcomes from ECLIPSE included a 55% TG reduction from baseline with evinacumab compared to a 4.6% reduction with placebo.[78] This large TG reduction may indicate potential use for patients with hypertriglyceridemia. In July 2020, evinacumab completed a phase 2 trial in 52 patients with severe hypertriglyceridemia. The primary endpoint was the percent change in TG from baseline to week 12.[81] Results from this phase 2 trial have not been released but will likely determine if a phase 3 trial will be conducted.

Another agent that targets ANGPTL3, vupanorsen (formerly known as IONIS-ANGPTL3-L_{Rx}), is an N-acetyl galactosamine-conjugated antisense oligonucleotide. A phase 1 trial in 44 healthy adults noted a 33.2-63.1% TG reduction after 6 weeks of subcutaneous vupanorsen (10, 20, 40, or 60 mg per week) with no serious adverse events.[82] A dose-ranging phase 2a trial evaluated the effect of vupanorsen on glucose, lipid metabolism, and liver fat in 105 participants with hypertriglyceridemia (TG > 150 mg/dL), T2DM (HbA1c 6.5-10%), and NAFLD.[83] The primary outcome of percent change from baseline TG at month 6 was statistically significant with 36%, 53%, and 47% reduction in vupanorsen 40 mg every 4 weeks, 80 mg every 4 weeks, and 20 mg weekly (P = .03, < .0001, .009), respectively, compared to 16% reduction in the placebo group. The most common side effects were mild injection site reactions.[84] Limitations to this trial include its small size and that only half of the population was receiving statin therapy at baseline.

Results from the phase 2a trial spurred the phase 2b **Ta**R**-**geting **A**NGPTL3 with an a**N**ti**S**ense o**L**igonucleotide in **A**dul**T**s with dyslipid**E**mia (TRANSLATE-TIMI 70) trial, estimated to enroll 260 participants with completion in January 2022. TRANSLATE-TIMI 70 will evaluate vupanorsen at 80, 120, 160 mg every 4 weeks and 60, 80, 120, 160 mg every 2 weeks in patients with a fasting non-HDL cholesterol ≥ 100 mg/dL, TG 150-500 mg/dL, and on a stable dose of a statin. The primary outcome is the percent change from baseline in non-HDL cholesterol at week 24, and secondary outcomes include percentage change from baseline in LDL-C and TG.[85]

A third agent targeting ANGPTL3 is ARO-ANG3, an investigational double-stranded, hepatocyte-targeted RNA interference trigger designed to inhibit ANGPTL3 mRNA expression.[86] ARO-ANG3 completed a phase 1 trial in July 2020, which evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of subcutaneous ARO-ANG3 in 52 healthy adults and dyslipidemic patients, including those with familial hypercholesterolemia and severe hypertriglyceridemia.[87] Results presented at the 2020 AHA Scientific Sessions noted that in patients with TG > 300 mg/dL at screening, ARO-ANG3 produced a 75% mean TG reduction that was sustained for at least 12 weeks after the second dose.[86] In January 2021, the manufacturer announced submission of an IND to the FDA to initiate a phase 2b dose-finding study in patients with mixed dyslipidemia.[88]

Herbals. Xuezhitong (XZT) is a traditional Chinese medicine that includes *Allium macrostemon Bunge*, also known as Xie Bai, a plant widely used to treat CVD in China.[89,90] Its antilipidemic mechanism of action is unknown but may be related to reverse cholesterol transport. Through this mechanism, the body eliminates excess cholesterol from nonhepatic peripheral tissues by transporting it to the liver for redistribution or removal through excretion into bile by the gallbladder.[89,91] HDL-C is the main lipoprotein involved in reverse cholesterol transport. In a study evaluating XZT effects in mice models fed high fat diets to mimic patients with atherosclerotic disease, XZT was noted to activate reverse cholesterol transport, increase HDL-C, and decrease LDL-C, TG, and total cholesterol.[89]

Subsequently, a double-blind, randomized trial conducted at 17 sites in China evaluated the effect of XZT in 358 adults with hypertriglyceridemia (TG 2.3-4.9 mmol/L, approximately 203-433 mg/dL). Patients received XZT 2700 mg/day, xuezhikang (XZK) 1200 mg/day, or placebo.[90] XZK is a lipid-lowering drug extracted from fermented yeast rice, contains lovastatin, and may lower LDL-C similarly to low-intensity statins (around 24-27%).[90,92] The primary endpoint of percent TG reduction over 12 weeks was statistically significant with a 30.7% reduction in the XZT group compared to 24% and 11.6% in the XZK and placebo groups, respectively. The authors noted similar tolerability profiles between the 3 groups with gastrointestinal side effects (dyspepsia, diarrhea, and abdominal discomfort) most commonly seen.[90] Although the results are promising, a longer study duration is needed to determine safety and results may be biased by the exclusion of patients with severe hypertriglyceridemia. Additionally, the trial did not evaluate cardiovascular risk reduction nor efficacy of XZT as an add-on to baseline statin therapy.

Conclusion

Currently, icosapent ethyl is the only FDA approved medication for cardiovascular risk reduction in patients with hypertriglyceridemia. However, generalizability of the results from REDUCE-IT are limited by the patient characteristics of the population studied. Results from phase 3 trials for CaPre (TRILOGY 1 and 2), pemafibrate (PROMINENT), and volanesorsen (COMPASS) as well as additional evidence from pipeline pharmacotherapies with novel mechanisms of actions (ApoC-III mRNA antisense inhibitors and ANGPTL3 antibodies) will help to guide future pharmacotherapy considerations for patients with hypertriglyceridemia.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

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

ORCID iDs

Jiashan Xu, PharmD https://orcid.org/0000-0002-6074-9692
Emily Ashjian, BCPS, BCACP, CDCES https://orcid.org/0000-0001-5746-0233

References

1. Grundy SM, Stone NJ, Bailey AL, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Circulation*. 2019;139(25):e1082-e1143.
2. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. *Circulation*. 2021;143(8):e254-e743.
3. Florentin M, Kostapanos MS, Anagnostis P, Liamis G. Recent developments in pharmacotherapy for hypertriglyceridemia: What's the current state of the art? *Expert Opin Pharmacother*. 2020;21(1):107-120.
4. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2011;123(20):2292-2333.
5. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3(2):213-219.
6. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*. 2007;298(3):299-308.
7. Vallejo-Vaz AJ, Corral P, Schreier L, Ray KK. Triglycerides and residual risk. *Curr Opin Endocrinol Diabetes Obes*. 2020;27(2):95-103.
8. Fruchart JC, Sacks FM, Hermans MP, et al. The residual risk reduction initiative: a call to action to reduce residual vascular

risk in dyslipidaemic patient. *Diab Vasc Dis Res*. 2008;5(4): 319-335.
9. Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet*. 2010;375(9726):1634-1639.
10. Virani SS, Morris PB, Agarwala A, et al. ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;78(9):960-993.
11. Valdivielso P, Ramirez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. *Eur J Intern Med*. 2014; 25(8):689-694.
12. Navina S, Acharya C, DeLany JP, et al. Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity. *Sci Transl Med*. 2011;3(107):107ra110.
13. Yang F, Wang Y, Sternfeld L, et al. The role of free fatty acids, pancreatic lipase and Ca+ signalling in injury of isolated acinar cells and pancreatitis model in lipoprotein lipase-deficient mice. *Acta Physiol*. 2009;195(1):13-28.
14. Skulas-Ray AC, Wilson PWF, Harris WS, et al. Omega-3 fatty acids for the management of hypertriglyceridemia: a science advisory from the American Heart Association. *Circulation*. 2019;140(12):e673-e691.
15. 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(14):1425-1435.
16. Faergeman O, Holme I, Fayyad R, et al. Plasma triglycerides and cardiovascular events in the treating to new targets and incremental decrease in end-points through aggressive lipid lowering trials of statins in patients with coronary artery disease. *Am J Cardiol*. 2009;104(4):459-463.
17. 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(4): 364-373.
18. Shapiro MD, Fazio S. Apolipoprotein B-containing lipoproteins and atherosclerotic cardiovascular disease. *F1000Res*. 2017;6:134.
19. Bradberry JC, Hilleman DE. Overview of omega-3 fatty acid therapies. *PT*. 2013;38(11):681-691.
20. Harris WS, Bulchandani D. Why do omega-3 fatty acids lower serum triglycerides? *Curr Opin Lipidol*. 2006;17(4):387-393.
21. Shearer GC, Savinova OV, Harris WS. Fish oil – how does it reduce plasma triglycerides? *Biochim Biophys Acta*. 2012; 1821(5):843-851.
22. Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2020;3:CD003177.
23. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for Hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22.
24. US Food & Drug Administration. FDA approves use of drug to reduce risk of cardiovascular events in certain adult patient groups. 2019. https://www.fda.gov/news-events/press-announcements/fda-approves-use-drug-reduce-risk-cardiovascular-events-certain-adult-patient-groups. Accessed March 30, 2021.
25. 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(1):94-106.
26. Blair HA, Dhillon S. Omega-3 carboxylic acids (Epanova): a review of its use in patients with severe hypertriglyceridemia. *Am J Cardiovasc Drugs*. 2014;14(5):393-400.
27. 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(10):1281-1288.
28. Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA*. 2020;324(22):2268-2280.
29. ClinicalTrials.gov. TRIal for efficacy of capre on hyper-TriglyceridemiA (TRIFECTA). October 20, 2011. https://www.clinicaltrials.gov/ct2/show/NCT01455844. Accessed February 4, 2021.
30. ClinicalTrials.gov. Assess the safety and efficacy of NKPL66 (CaPre™) in the treatment of mild-to-high hypertriglyceridemia. January 24, 2012. https://clinicaltrials.gov/ct2/show/NCT01516151. Accessed February 4, 2021.
31. Acasti Pharma. Form 10-K. Annual report persuant to section 13 and 15(d) of the Securities Exchange Act of 1934. June 29, 2020. https://www.acastipharma.com/en/investors/regulatory-filings/annual-reports/content/0001171843-20-004613/0001171843-20-004613.pdf. Accessed March 30, 2021.
32. ClinicalTrials.gov. A Phase 3 STudy of CaPRe in LOwering Very hiGh TriglYcerides (TRILOGY 1). January 12, 2018. https://www.clinicaltrials.gov/ct2/show/NCT03398005. Accessed February 4, 2021.
33. ClinicalTrials.gov. A Phase 3 STudy of CaPRe in LOwering Very hiGh TriglYcerides (TRILOGY 2). December 5, 2017. https://www.clinicaltrials.gov/ct2/show/NCT03361501. Accessed February 4, 2021.
34. Acasti Pharma. Acasti pharma reports topline results for TRILOGY 1 phase 3 trial of CaPre. January 13, 2020. https://www.acastipharma.com/en/investors/news-events/press-releases/detail/173/acasti-pharma-reports-topline-results-for-trilogy-1-phase-3. Accessed March 30, 2021.
35. Acasti Pharma. Acasti pharma provides update on TRILOGY 1 and TRILOGY 2 phase 3 trials of CaPre. February 10, 2020. https://www.acastipharma.com/en/investors/news-events/press-releases/detail/174/acasti-pharma-provides-update-on-trilogy-1-and-trilogy-2. Accessed March 30, 2021.
36. Acasti Pharma. Acasti pharma reports topline triglyceride results from phase 3 TRILOGY 2 study of CaPre in patients with severe hypertriglyceridemia. August 31, 2020. https://www.acastipharma.com/en/investors/news-events/press-releases/detail/186/acasti-pharma-reports-topline-triglyceride-results-from. Accessed March 30, 2021.

37. Climax J, Newsome PN, Hamza M, et al. Effects of Epeleuton, a novel synthetic second-generation n-3 fatty acid, on non-alcoholic fatty liver disease, triglycerides, glycemic control, and cardiometabolic and inflammatory markers. *J Am Heart Assoc*. 2020;9(16)-e016334.
38. ClinicalTrials.gov. Safety and efficacy study of orally administered DS102 in healthy subjects. February 4, 2016. https://clinicaltrials.gov/ct2/show/NCT02673593. Accessed February 4, 2021.
39. ClinicalTrials.gov. TRIgyceride and glucose control with epeleuton in metabolic syndrome patients (TRIAGE). April 28, 2020. https://www.clinicaltrials.gov/ct2/show/NCT04365400. Accessed February 4, 2021.
40. Triglide (fenofibrate) [prescribing information]. East Brunswick, NJ: Casper Pharma LLC; 2021.
41. Fenoglide (fenofibrate) [prescribing information]. Bridgewater, NJ: Salix Pharmaceuticals; 2021.
42. Tricor (fenofibrate) [prescribing information]. North Chicago, IL: AbbVie Inc.; 2021.
43. Lopid (gemofibrozil) [prescribing information]. New York, NY: Parke-Davis; 2020.
44. Fruchart JC, Santos RD, Aguilar-Salinas C, et al. The selective peroxisome proliferator-activated receptor alpha modulator (SPPARMalpha) paradigm: conceptual framework and therapeutic potential : A consensus statement from the International Atherosclerosis Society (IAS) and the Residual Risk Reduction Initiative (R3i) Foundation. *Cardiovasc Diabetol*. 2019;18(1):71.
45. Fruchart JC. Pemafibrate (K-877), a novel selective peroxisome proliferator-activated receptor alpha modulator for management of atherogenic dyslipidaemia. *Cardiovasc Diabetol*. 2017;16(1):124.
46. 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(8):754-772.
47. 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.
48. 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(1):173-184.
49. 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(6):521-538.
50. 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.
51. 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(3):538-546.
52. Araki E, Yamashita S, Arai H, et al. Efficacy and safety of pemafibrate in people with type 2 diabetes and elevated triglyceride levels: 52-week data from the PROVIDE study. *Diabetes Obes Metab*. 2019;21(7):1737-1744.
53. 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.
54. ClinicalTrials.gov. Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes (PROMINENT). March 7, 2017. https://clinicaltrials.gov/ct2/show/NCT03071692. Accessed February 4, 2021.
55. Blair HA. Pemafibrate: first global approval. *Drugs*. 2017;77(16):1805-1810.
56. Pharmaceuticals and Medical Devices Agency (PMDA). Report on the deliberation results. May 17, 2017. https://www.pmda.go.jp/files/000226672.pdf. Accessed May 25, 2021.
57. Norata GD, Tsimikas S, Pirillo A, Catapano AL. Apolipoprotein C-III: from pathophysiology to pharmacology. *Trends Pharmacol Sci*. 2015;36(10):675-687.
58. Taskinen MR, Boren J. Why is apolipoprotein CIII emerging as a novel therapeutic target to reduce the burden of cardiovascular disease? *Curr Atheroscler Rep*. 2016;18(10):59.
59. Qamar A, Khetarpal SA, Khera AV, Qasim A, Rader DJ, Reilly MP. Plasma apolipoprotein C-III levels, triglycerides, and coronary artery calcification in type 2 diabetics. *Arterioscler Thromb Vasc Biol*. 2015;35(8):1880-1888.
60. Witztum JL, Gaudet D, Freedman SD, et al. Volanesorsen and triglyceride levels in familial chylomicronemia syndrome. *N Engl J Med*. 2019;381(6):531-542.
61. Endocrinologic and Metabolic Drugs Advisory Committee (Food and Drug Administration). EMDAC Meeting for Volanesorsen (Waylivra). 2018. https://www.fda.gov/advisory-committees/endocrinologic-and-metabolic-drugs-advisory-committee/2018-meeting-materials-endocrinologic-and-metabolic-drugs-advisory-committee. Accessed April 9, 2021.
62. European Medicines Agency (EMA). First treatment for rare disease characterised by high levels of triglycerides in blood. 2019. https://www.ema.europa.eu/en/news/first-treatment-rare-disease-characterised-high-levels-triglycerides-blood. Accessed December 10, 2020
63. European Medicines Agency (EMA). Waylivra, Volanesorsen - Product Information. 2019. https://www.ema.europa.eu/en/documents/product-information/waylivra-epar-product-information_en.pdf. Accessed May 25 2021.
64. ClinicalTrials.gov. The COMPASS Study: a Study of Volanesorsen (Formally ISIS-APOCIIIRx) in Patients With Hypertriglyceridemia. November 24, 2014. https://clinicaltrials.gov/ct2/show/NCT02300233. Accessed April 9, 2021.

65. Gouni-Berthold I, Alexander VJ, Yang Q, et al. Efficacy and safety of volanesorsen in patients with multifactorial chylomicronaemia (COMPASS): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol*. 2021;9(5):264-275.
66. ClinicalTrials.gov. Study of ISIS 678354 (AKCEA-APOCIII-LRx) in participants with hypertriglyceridemia and established Cardiovascular Disease (CVD). December 28, 2017. https://clinicaltrials.gov/ct2/show/NCT03385239. Accessed April 9, 2021.
67. Alexander VJ, Xia S, Hurh E, et al. N-acetyl galactosamine-conjugated antisense drug to APOC3 mRNA, triglycerides and atherogenic lipoprotein levels. *Eur Heart J*. 2019;40(33):2785-2796.
68. ClinicalTrials.gov. Safety, tolerability, PK, and pharmacodynamics(PD) of IONIS APOCIII-LRx in healthy volunteers with elevated triglycerides. September 14, 2016. https://clinicaltrials.gov/ct2/show/NCT02900027. Accessed April 9, 2021.
69. Ionis Pharmaceuticals. Positive phase 2 clinical data of AKCEA-APOCIII-L(Rx) presented at ESC congress 2020. August 29, 2020. https://ir.ionispharma.com/news-releases/news-release-details/positive-phase-2-clinical-data-akcea-apociii-lrx-presented-esc-0. Accessed April 9, 2021.
70. Ionis Pharmaceuticals. Ionis announces initiation of the global Phase 3 BALANCE study for AKCEA-APOCIII-LRX in patients with familial chylomicronemia syndrome. December 1, 2020. https://ir.ionispharma.com/news-releases/news-release-details/ionis-announces-initiation-global-phase-3-balance-study-akcea. Accessed April 9, 2021.
71. ClinicalTrials.gov. A study of AKCEA-APOCIII-LRx administered to patients with Familial Chylomicronemia Syndrome (FCS) (BALANCE). September 29, 2020. https://clinicaltrials.gov/ct2/show/NCT04568434. Accessed April 9, 2021.
72. ClinicalTrials.gov. Study of ARO-APOC3 in healthy volunteers, hypertriglyceridemic patients and patients with Familial Chylomicronemia Syndrome (FCS). December 21, 2018. https://clinicaltrials.gov/ct2/show/NCT03783377. Accessed April 9, 2021.
73. Arrowhead Pharmaceuticals. Events & Presentations - Pharmacodynamic effect of ARO-APOC3, an investigational hepatocyte-targeted RNA interference therapeutic targeting apolipoprotein C3, in patients with hypertriglyceridemia and multifactorial chylomicronemia. 2021. https://ir.arrowheadpharma.com/static-files/92ed0c31-9a6b-4e75-8afa-77ae687881f5. Accessed March 30, 2021.
74. Arrowhead Pharmaceuticals. Arrowhead pharmaceuticals files IND to begin phase 2b study of ARO-APOC3 in patients with severe hypertriglyceridemia. March 1, 2021. https://ir.arrowheadpharma.com/news-releases/news-release-details/arrowhead-pharmaceuticals-files-ind-begin-phase-2b-study-aro. Accessed April 9, 2021.
75. ClinicalTrials.gov. Study to evaluate ARO-APOC3 in adults with severe hypertriglyceridemia. January 22, 2021. https://clinicaltrials.gov/ct2/show/NCT04720534. Accessed April 9, 2021.
76. Tikka A, Jauhiainen M. The role of ANGPTL3 in controlling lipoprotein metabolism. *Endocrine*. 2016;52(2):187-193.
77. Stitziel NO, Khera AV, Wang X, et al. ANGPTL3 deficiency and protection against coronary artery disease. *J Am Coll Cardiol*. 2017;69(16):2054-2063.
78. Raal FJ, Rosenson RS, Reeskamp LF, et al. Evinacumab for homozygous familial hypercholesterolemia. *N Engl J Med*. 2020;383(8):711-720.
79. Mytilinaiou M, Kyrou I, Khan M, Grammatopoulos DK, Randeva HS. Familial hypercholesterolemia: New Horizons for diagnosis and effective management. *Front Pharmacol*. 2018;9:707.
80. US Food & Drug Administration. FDA approves add-on therapy for patients with genetic form of severely high cholesterol. 2021. https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-add-therapy-patients-genetic-form-severely-high-cholesterol. Accessed March 30, 2021.
81. ClinicalTrials.gov. Safety and efficacy following repeat-dose of evinacumab (anti-ANGPTL3) in patients with severe hypertriglyceridemia (sHTG) at risk for acute pancreatitis. March 2, 2018. https://clinicaltrials.gov/ct2/show/NCT03452228. Accessed March 30, 2021.
82. Graham MJ, Lee RG, Brandt TA, et al. Cardiovascular and metabolic effects of ANGPTL3 antisense oligonucleotides. *N Engl J Med*. 2017;377(3):222-232.
83. ClinicalTrials.gov. Study of ISIS 703802 in participants with hypertriglyceridemia, type 2 diabetes mellitus, and nonalcoholic fatty liver disease. December 13, 2017. https://clinicaltrials.gov/ct2/show/results/NCT03371355. Accessed April 9, 2021.
84. Gaudet D, Karwatowska-Prokopczuk E, Baum SJ, et al. Vupanorsen, an N-acetyl galactosamine-conjugated antisense drug to ANGPTL3 mRNA, lowers triglycerides and atherogenic lipoproteins in patients with diabetes, hepatic steatosis, and hypertriglyceridaemia. *Eur Heart J*. 2020;41(40):3936-3945.
85. ClinicalTrials.gov. A dose-ranging study with vupanorsen (TRANSLATE-TIMI 70). August 18, 2020. https://clinicaltrials.gov/ct2/show/NCT04516291. Accessed April 9, 2021.
86. Arrowhead Pharmaceuticals. Events & presentations - pharmacodynamic effect of ARO-ANG3, an investigational RNA interference therapeutic targeting hepatic angiopoietin-like protein 3, in patients with dyslipidemia. 2021. https://ir.arrowheadpharma.com/static-files/28208c1f-4308-47a3-8b60-906e658756c6. Accessed March 30, 2021
87. Clinicaltrials.gov. Study of ARO-ANG3 in healthy volunteers and in dyslipidemic patients. November 20, 2018. https://clinicaltrials.gov/ct2/show/NCT03747224. Accessed April 9, 2021.
88. Arrowhead Pharmaceuticals. Arrowhead pharmaceuticals files IND for phase 2b study of ARO-ANG3 for treatment of mixed dyslipidemia. March 1, 2021. https://ir.arrowheadpharma.com/news-releases/news-release-details/arrowhead-pharmaceuticals-files-ind-phase-2b-study-aro-ang3. Accessed April 9, 2021.
89. Meng XB, Zhu T, Yang DH, Liang W, Sun GB, Sun XB. Xuezhitong capsule, an extract of Allium macrostemon

Bunge, exhibits reverse cholesterol transport and accompanies high-density lipoprotein levels to protect against hyperlipidemia in ApoE(-/-) mice. *Ann Transl Med*. 2019;7(11):239.

90. Jia W, Li Y, Wan J, et al. Effects of Xuezhitong in patients with hypertriglyceridemia: a multicentre, randomized, double-blind, double simulation, positive drug and placebo parallel control study. *Cardiovasc Drugs Ther*. 2020;34(4):525-534.
91. Marques LR, Diniz TA, Antunes BM, et al. Reverse cholesterol transport: molecular mechanisms and the non-medical approach to enhance HDL cholesterol. *Front Physiol*. 2018;9:526.
92. Moriarty PM, Roth EM, Karns A, et al. Effects of Xuezhikang in patients with dyslipidemia: a multicenter, randomized, placebo-controlled study. *J Clin Lipidol*. 2014;8(6):568-575.
93. Vascepa (icosapent ethyl) [prescribing information]. Bridgewater, NJ: Amarin Pharma, Inc; 2019.