A ANNUAL REVIEWS

ANNUAL CONNECT

www.annualreviews.org

- Download figures
- Navigate cited references
- Keyword search
- Explore related articles
- Share via email or social media

Annu. Rev. Med. 2021. 72:431-46

First published as a Review in Advance on November 20, 2020

The Annual Review of Medicine is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-100119-013612

Copyright © 2021 by Annual Reviews. All rights reserved

Annual Review of Medicine

New Approaches for the Prevention and Treatment of Cardiovascular Disease: Focus on Lipoproteins and Inflammation

Aliza Hussain and Christie M. Ballantyne

Department of Medicine, Baylor College of Medicine, Houston, Texas 77030, USA; email: aliza.hussain@bcm.edu, cmb@bcm.edu

Keywords

bempedoic acid, canakinumab, icosapent ethyl, inclisiran, inflammation, lipoprotein(a), triglyceride-rich lipoproteins

Abstract

Although numerous trials have convincingly shown benefits of statin therapy in both primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD), most showed relative risk reductions of 25–40%, and thus many individuals continue to have ASCVD events despite statin therapy. Substantial progress has been made in developing therapies that address the residual risk for ASCVD despite statin therapy. In this review, we summarize progress of currently available therapies along with therapies under development that further reduce low-density lipoprotein cholesterol and apolipoprotein B–containing lipoproteins, reduce lipoprotein(a), reduce ASCVD events in patients with high triglycerides, and directly target inflammation to reduce ASCVD risk.

INTRODUCTION

Elevated low-density lipoprotein cholesterol (LDL-C) is a well-known risk factor for atherosclerotic cardiovascular disease (ASCVD) (1). A large meta-analysis of landmark statin clinical trials showed that more intensive LDL-C-lowering therapy provided greater reduction in ASCVD events (2). Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was the first trial to show that additional LDL-C lowering with ezetimibe reduced cardiovascular events compared with statin alone (3). Two other trials, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) (4) and Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome during Treatment with Alirocumab (ODYSSEY OUTCOMES) (5), demonstrated that substantial LDL-C lowering beyond that obtained with statin monotherapy provided additional reduction in ASCVD risk and further validated the hypothesis that lowering LDL-C leads to reduction in ASCVD events. These studies, in aggregate, were the basis for the recommendations of the American Heart Association/American College of Cardiology (AHA/ACC) Guideline for the Management of Blood Cholesterol (2018) (6) and the European Society of Cardiology/European Atherosclerosis Society Guidelines for the Management of Dyslipidaemias (2019) (7) to use high-intensity statin therapy in all individuals with established ASCVD, with consideration of additional, nonstatin therapy if LDL-C remains above 100 mg/dl (70 mg/dl in higher-risk patients).

However, even in individuals treated with optimal statin and other evidence-based lipidlowering therapy, considerable residual ASCVD risk persists (2). In the recent past, we have seen dramatic progress toward identifying determinants of this residual cardiovascular risk. It may reflect atherogenic apolipoprotein (apo) B–containing particles besides LDL, including triglyceride (TG)–rich lipoproteins and lipoprotein(a), which are not reflected in LDL-C level. The Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), which evaluated the addition of icosapent ethyl (IPE) to optimal statin therapy, demonstrated dramatic reduction in cardiovascular events, not only in patients with known ASCVD, but also in patients with diabetes who had multiple risk factors and residual hypertriglyceridemia (8).

Atherosclerosis is an inflammatory process. The past decade has ushered in a renewed interest in the role of inflammation in ASCVD prevention, including the landmark Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), which provided clinical proof of concept that an anti-inflammatory agent could result in significant ASCVD risk reduction beyond that obtained by reducing LDL-C (9).

In this review, we focus on key advances in preventive cardiology for the treatment and prevention of ASCVD. In particular, we discuss recent LDL-C-lowering therapies that are currently available or in clinical trials, emerging approaches to target non-LDL-C lipid parameters such as TG and lipoprotein(a), and immune-modulatory therapies targeting atherosclerosis that have recently been tested in clinical trials or are currently in development (**Figure 1**). Other approaches to address residual risk, such as more-aggressive reductions in blood pressure, new treatments for diabetes, and lifestyle changes with diet, have also shown benefit and are critical for optimal reduction of not only ASCVD but also heart failure but are beyond the scope of this review.

NEW THERAPIES TARGETING LDL-C

PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are monoclonal antibodies (mAbs) that inactivate extracellular PCSK9 and prevent binding of PCSK9 to the LDL receptor. When PCSK9 binds to the LDL receptor and undergoes endocytosis, the complex is targeted

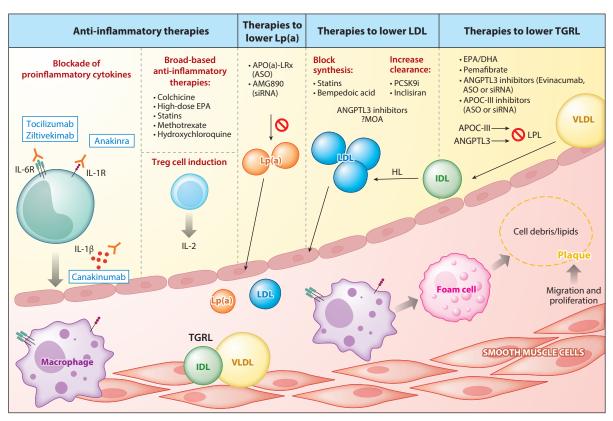


Figure 1

Current and emerging therapies target diverse atherosclerotic processes to reduce residual risk for atherosclerotic cardiovascular disease events. To address residual risk for cardiovascular events that persists despite guideline-recommended statin therapy, newer agents offer alternative mechanisms to lower low-density lipoprotein cholesterol, and advances in our understanding of atherogenesis and atherothrombosis provide emerging approaches to target other lipid and nonlipid parameters such as triglyceride and triglyceride-rich lipoproteins, lipoprotein(a), and inflammation. Abbreviations: ANGPTL3, angiopoietin-like protein 3; APO, apolipoprotein; ASO, antisense oligonucleotide; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HL, hepatic lipase; IDL, intermediate-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; MOA, mechanism of action; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; siRNA, small interfering ribonucleic acid; TGRL, triglyceride-rich lipoprotein; Treg, regulatory T cell; VLDL, very-low-density lipoprotein.

to the lysosome with degradation of the LDL receptor. In contrast, inhibition of PCSK9 binding to the LDL receptor allows recycling of the receptor to the cell surface. Therefore, injection of mAbs that inhibit PCSK9 increases LDL receptors and decreases LDL-C level. PCSK9 inhibitors provide consistent and substantial LDL-C reductions of up to 60–70% (10).

Both evolocumab and alirocumab have demonstrated significant reductions in cardiovascular events (4, 5). In FOURIER, a linear relationship was observed between LDL-C level achieved and adverse cardiovascular events, with ASCVD reduction seen down to lowest levels of LDL-C (<20 mg/dl) without increase in adverse safety events (11). Furthermore, a prespecified secondary analysis of FOURIER demonstrated that the benefit of evolocumab may be greater if total events rather than first events were taken into account (12). Based on the positive results of these trials, use of evolocumab and alirocumab was approved by the US Food and Drug Administration (FDA) and endorsed by major multisociety preventive cardiology guidelines in the United States (2018)

(6) and Europe (2019) (7) for reduction of both LDL-C and ASCVD event risk in individuals with established ASCVD.

Multiple post hoc analyses of FOURIER and ODYSSEY OUTCOMES provide further support for the use of PCSK9 inhibitor therapy in individuals with ASCVD, with enhanced benefit seen in higher-risk subgroups. In FOURIER, patients with peripheral artery disease (13), more-recent myocardial infarction (MI), multiple prior MIs, or residual coronary disease (14) had greater absolute reductions in risk for cardiovascular death, MI, or stroke with evolocumab. Moreover, while LDL-C reduction with evolocumab reduced cardiovascular events across all high-sensitivity C-reactive protein (hsCRP) strata (<1, 1–3, and >3 mg/L), greater absolute risk reductions were seen in patients with higher baseline hsCRP (15). Finally, a 27–single-nucleotide polymorphism (SNP) genetic risk score was calculated to categorize FOURIER subjects into low-risk, intermediate-risk, and high-risk subgroups in a nested-cohort study. Individuals with higher genetic risk derived greater absolute and relative cardiovascular risk reduction with evolocumab compared with individuals in low- or intermediate-risk categories (16).

Likewise, in post hoc analyses of ODYSSEY OUTCOMES, substantially greater absolute reductions in cardiovascular endpoints were demonstrated in patients stratified as very high risk for future ASCVD events as defined by the 2018 AHA/ACC guidelines (~63% of the study population) (6, 17), patients who received coronary artery bypass grafting after acute coronary syndrome (18), and patients with polyvascular disease (two or three arterial beds) (19).

The recently published Evolocumab for Early Reduction of LDL Cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS) is the first trial to establish safety and efficacy of a PCSK9 inhibitor, evolocumab, initiated during the in-hospital phase of acute coronary syndrome. Evolocumab substantially reduced LDL-C by 40% compared with placebo, and adverse events were similar in both groups (20). In the open-label, single-arm Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects with Genetic LDL Disorders (TAUSSIG), evolocumab was well tolerated and effectively reduced plasma LDL-C levels in patients with homozygous familial hypercholesterolemia (HoFH; by 21%) or severe heterozygous familial hypercholesterolemia (HeFH; by 55%) over a median follow-up of 4.1 years (21). In the longest-duration (5 years) study of a PCSK9 inhibitor, the Open Label Study of Long Term Evaluation Against LDL-C Trial (OSLER-1), evolocumab demonstrated excellent long-term safety and tolerability during open-label treatment (22).

The most common adverse effects of PCSK9 inhibitor therapy reported in the large outcomes study were injection-site reactions, flu-like illness, nasopharyngitis, and upper respiratory tract infection. The most common adverse events that led to discontinuation of the study drug were allergic reactions (for alirocumab) and myalgia, nausea, and dizziness (for evolocumab).

In conclusion, multiple recent clinical trials, including post hoc analyses, of mAbs against PCSK9, namely evolocumab and alirocumab, have provided additional evidence regarding greater absolute benefit in higher-risk groups, long-term safety for up to 5 years, safety and tolerability during the in-hospital phase of acute coronary syndrome, and safety and efficacy in individuals with HeFH or HoFH.

Bempedoic Acid

Bempedoic acid is an oral nonstatin therapy that primarily blocks cholesterol biosynthesis in the liver by inhibiting adenosine triphosphate citrate lyase (ACL), an enzyme upstream from HMG-CoA reductase. This also results in LDL receptor upregulation and increased clearance of LDL. Bempedoic acid is administered as a prodrug that is converted to its active moiety by the enzyme ACSVL1, which is present in hepatocytes but not present in skeletal muscle (23). Therefore, bempedoic acid may have less potential to cause muscle side effects.

A total of five randomized double-blind placebo-controlled multicenter phase III clinical trials—known as Cholesterol Lowering via Bempedoic Acid, an ACL-inhibiting Regimen (CLEAR) trials—have established safety, tolerability, and LDL-C-lowering efficacy of bempedoic acid (four trials) or bempedoic acid/ezetimibe combination tablet (one trial). In the largest of these trials, CLEAR Harmony, conducted in 2,230 patients with ASCVD and/or HeFH on background statin therapy (85% using moderate- or high-intensity statin), addition of bempedoic acid resulted in reduction of LDL-C by 16.5% compared with placebo over 1-year follow-up. The incidence of gout and adverse events resulting in drug discontinuation were higher in the bempedoic acid group than in the placebo group (24). Bempedoic acid can increase levels of uric acid, which in some patients may lead to gout, and thus may merit monitoring especially in patients with a past history of gout or elevated uric acid.

CLEAR Tranquility, conducted in 301 patients with hypercholesterolemia and ASCVD and/or HeFH who were on maximally tolerated statin (37% on high-intensity statin), evaluated the use of a bempedoic acid/ezetimibe combination tablet. The combination resulted in reduction of LDL-C by 38% compared with placebo, with a safety profile similar to that of placebo (25). The results from these trials are the basis for the approval of bempedoic acid by the FDA in February 2020 for use in patients with HeFH or established ASCVD on maximally tolerated statin therapy who require additional LDL-C lowering. Bempedoic acid is the first oral nonstatin drug to be approved for this indication since 2002.

The effects of bempedoic acid therapy on cardiovascular outcomes have not been established. CLEAR Outcomes (NCT02993406), a randomized double-blind placebo-controlled study that has enrolled 14,032 patients, will assess cardiovascular events over an estimated follow-up of 4.75 years to answer this question.

Inclisiran

Inclisiran represents an alternative approach to mediate durable and potent reductions in LDL-C. It is a small interfering ribonucleic acid (siRNA) that silences messenger RNA (mRNA) in hepatocytes, preventing translation of PCSK9 (26). It is conjugated to N-acetylgalactosamine carbohydrate (GalNAc), which specifically binds to asialoglycoprotein receptors on hepatocytes with high affinity, leading to the uptake of drug into hepatocytes. As a result, lower drug doses can achieve similar efficacy, limiting systemic toxicity (27).

Three phase III double-blind randomized clinical trials designed to evaluate the safety and efficacy of twice-yearly inclisiran (300 mg) injections have been completed. ORION-10 enrolled patients with ASCVD (n = 1,561) in the United States, whereas ORION-11 enrolled patients with ASCVD or ASCVD risk equivalent (n = 1,617) in Europe, on maximally tolerated statin therapy. In ORION-10, inclisiran reduced LDL-C by 52% compared with placebo at day 510, and in ORION-11, an LDL-C reduction of 50% compared with placebo was seen at day 510. Adverse events were similar with both drug and placebo, except for injection-site reactions, which were more common with inclisiran (28). In a prespecified exploratory analysis, fewer patients treated with inclisiran had cardiovascular events (MI and stroke) compared with placebo (28). ORION-9, which enrolled 482 patients with HeFH on optimal statin and ezetimibe therapy, showed that inclisiran reduced LDL-C by 48% compared with placebo at day 510. Adverse events and serious adverse events were similar in the two groups (29).

All three studies, together, demonstrate that inclisiran can achieve robust and sustained reductions in LDL-C and PCSK9 levels with a frequency of side effects comparable to placebo. Inclisiran provides reductions in LDL-C that are similar to those obtained with PCSK9 mAbs and persist at 1-year follow-up (30). While a long-acting injection requiring twice-yearly administration seems promising, an ongoing cardiovascular outcomes trial of inclisiran, ORION-4 (n = 15,000), will provide conclusive evidence on long-term safety and clinical efficacy (NCT03705234).

NEW THERAPIES TARGETING TRIGLYCERIDE PATHWAYS

Omega-3 Fatty Acids

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two major types of omega-3 fatty acids. Numerous studies show that omega-3 fatty acids decrease elevated TG and very-low-density lipoprotein (VLDL) levels. These effects are seen with high doses (>2 to 4 g/day). DHA may increase LDL-C levels; EPA generally has no effect on LDL-C. Newer formulations of omega-3 fatty acids, the subject of recently completed and ongoing clinical trials, include EPA alone and combined EPA and DHA.

REDUCE-IT evaluated the use of icosapent ethyl (IPE), highly purified EPA, in 8,179 highrisk patients (either with established ASCVD or with diabetes and one other ASCVD risk factor) who had persistent hypertriglyceridemia (135–499 mg/dl) on maximally tolerated statin therapy (8). Over a 5-year follow-up, IPE (4 g/day) significantly reduced major ASCVD events by 25% and prespecified secondary ASCVD endpoints of fatal/nonfatal MI by 31%, fatal/nonfatal stroke by 28%, and cardiovascular mortality by 20%. Important adverse events included absolute excess of atrial fibrillation (by 1.4% more than placebo) and peripheral edema (by 1.5% more than placebo). The increase in bleeding risk with IPE was not statistically significant (8). A follow-up secondary analysis found that IPE provided even greater cardiovascular risk reduction when first, subsequent, and total cardiovascular events were included (31).

Based on the results of this landmark clinical trial, multiple societies, including the American Diabetes Association (32), European Society of Cardiology/European Atherosclerosis Society (7), and National Lipid Association (33), endorsed the use of IPE for reduction in risk of future ASCVD events in individuals with ASCVD and/or diabetes (with other risk factors) and hyper-triglyceridemia on maximally tolerated statin therapy. In December 2019, IPE became the first non-LDL-lowering lipid drug to receive an indication for ASCVD event risk reduction (in patients with ASCVD already on statin therapy) from the FDA.

In REDUCE-IT, TG was reduced by a net of 15%, non-high-density lipoprotein cholesterol (non-HDL-C) by 9%, and apo B by 10% in the IPE group compared with placebo (8). Kastelein & Stroes (34) reported that the reduction in non-HDL-C observed in REDUCE-IT would be expected to lower ASCVD risk by only about 6–8%. Therefore, the effects on lipids cannot fully explain the overall ASCVD risk reduction seen in the study. Possible other mechanisms to explain the beneficial effects of IPE seen in REDUCE-IT are antiplatelet effects, anti-inflammatory effects, and effects on endothelial function (35).

Multiple studies support the anti-inflammatory effects of IPE. In MARINE and ANCHOR, IPE at 4 g/day significantly lowered levels of the proinflammatory compounds lipoproteinassociated phospholipase A2 (Lp-PLA2), oxidized LDL, and hsCRP (36, 37). In addition, omega-3 fatty acids have been shown to increase production of resolvins, which play an important role in counter-regulation of inflammation (38). Optical coherence tomography demonstrated that patients randomized to IPE (1.8 g/day) had greater increase in fibrous cap thickness and decrease in macrophage accumulation at 9-month follow-up after percutaneous coronary intervention (39). Taken together, the combined evidence suggests that anti-inflammatory effects of IPE may have contributed to the cardiovascular benefits observed in REDUCE-IT.

Interim results of the Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy (EVAPORATE) trial demonstrated that in 80 patients with known angiographic coronary artery disease on statins (LDL-C >40 and <115 mg/dl) and

hypertriglyceridemia (135–499 mg/dl) randomized 1:1 to IPE or placebo, IPE did not reduce the primary endpoint of low attenuation plaque volume but reduced total plaque volume as assessed by coronary computed tomography angiography over 9 months of follow-up (40).

Statin Residual Risk Reduction with Epanova in High CV Risk Patients with Hypertriglyceridemia (STRENGTH), a phase III trial evaluating use of 4 g/day of EPA + DHA carboxylic acids in patients with elevated TG levels (\geq 180 and <500 mg/dl) and low HDL-C (<42 mg/dl for men and <47 mg/dl for women), was stopped earlier than planned based on the January 2020 recommendation of an independent Data Monitoring Committee because of low likelihood of demonstrating cardiovascular benefit (NCT02104817). It is hoped that results from the trial, which are yet to be published, will help clarify whether the lack of benefit was due to the use of combined EPA and DHA rather than EPA alone, the formulation of EPA + DHA used (i.e., carboxylic acid), or other mechanisms not yet known.

Ongoing outcomes trials evaluating the use of omega-3 fatty acids include Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and Eicosapentaenoic Acid (RESPECT-EPA; UMIN000012069) and Omega-3 Fatty Acids in Elderly Patients with Acute Myocardial Infarction (OMEMI; NCT01841944). RESPECT-EPA will primarily be conducted in Japan and will evaluate the use of lower-dose EPA (1.8 g/day) in patients with ASCVD on statin therapy irrespective of TG levels. OMEMI is studying EPA + DHA (1.8 g/day) in elderly patients (aged 70–82 years) in Norway diagnosed with acute MI.

Pemafibrate

Fibrates are effective therapy for TG lowering; however, the use of fenofibrate as add-on therapy to statins has not consistently shown cardiovascular benefit. Post hoc analyses of clinical trials of fenofibrate have, however, demonstrated that individuals with higher levels of TG and lower HDL-C derived significant cardiovascular risk reduction (41, 42). Pemafibrate, a selective peroxisome proliferator–activated receptor– α modulator, was designed to lower TG (by about 30%) while minimizing side effects (43). The Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial aims to evaluate the use of pemafibrate in combination with maximally tolerated statins in patients with diabetes and elevated TG levels (200–499 mg/dl) and low HDL-C (\leq 40 mg/dl) and is planned to reach completion in 2022 (NCT03071692).

Apo C-III

Lipoprotein lipase (LPL) plays an important role in the metabolism of TG and TG-rich lipoproteins in the circulation. Apo C-III and angiopoietin-like protein 3 (ANGPTL3) have been shown to modulate LPL activity and consequently affect TG levels. Evidence from genomic studies shows that polymorphisms of the genes encoding these proteins are associated with reduced risk for ASCVD (44, 45). Accordingly, considerable interest has been shown in the development of therapeutic approaches targeting these factors.

RNA interference therapies such as antisense oligonucleotides (ASOs) and siRNA, which bind to and promote the degradation of *APOC3* mRNA, have shown profound and durable reduction in TG (**Table 1**). Volanesorsen (formerly IONIS-ApoCIII_{Rx} and ISIS-ApoCIII_{Rx}), an ASO targeting apo C-III, was approved in Europe but not in the United States for the treatment of familial chylomicronemia syndrome. Conjugation of a newer generation of ASO against apo C-III (APOCIII-L_{Rx}) and siRNA against apo C-III with GalNAc allows lower doses of drug to be used to achieve similar efficacy and attenuates off-target side effects such as thrombocytopenia. Robust clinical programs are ongoing for these agents.

Table 1	Emerging	therapies	for treatment	of dyslipidemia
---------	----------	-----------	---------------	-----------------

Drug	Mechanism	Clinical trial stage, patient population, reference	Results	Status/future directions	
Volanesorsen	ASO targeting apoC-III	Phase III. Patients with FCS (n = 66); volanesorsen 300 mg/wk versus placebo (46)	 apoC-III: -84% (3 mo); -83% (6 mo) TG: -76% (3 mo); -53% (6 mo); -40% (1 yr) Safety: ISR and thrombocytopenia notable side effects; high rates of drug discontinuation and nonserious bleeding with drug 	Approved by EMA for TG-lowering in FCS on May 3, 2019 (47), but not approved by FDA	
AKCEA- APOCIII- L _{Rx}	ASO targeting apoC-III ^a	Phase I/IIa. Healthy adults with TG \geq 90 mg/dl in SADS ($n = 40$) and \geq 200 mg/dl in MADS ($n = 27$) (48)	SADS: mean change (dose): apoC-III: -4% (10 mg); -32% (30 mg); -65% (60 mg); -78% (90 mg); -91% (120 mg) TG: -12% (10 mg); -11% (30 mg); -43% (60 mg); -68% (90 mg); -77% (120 mg) MADS: mean change (dose): apoC-III: -66% (15 mg/wk); -84% (30 mg/wk); -89% (60 mg/wk) after 6 wk TG: -59% (15 mg/wk); -73% (30 mg/wk); -66% (60 mg/4 wk) after 6 wk Safety: 1 ISR, no platelet count reductions (NCT02900027)	Phase II study ongoing in patients with HTG and ASCVD (NCT03385239)	
ARO- APOC3	siRNA targeting apoC-III ^a	Phase I/IIa. SADS in healthy adults (n = 40) with TG > 80 mg/dl (49)	Mean max change: ApoC-III: -72% (10 mg) to -94% (100 mg) TG: -53% (10 mg) to -64% (100 mg) LDL-C: -12% (25 mg) to -25% (10 mg) HDL-C: +30% (10 mg) to +69% (100 mg); reductions maintained at wk 16 Safety: 8 ISR; no SAE reported	Phase I study ongoing in healthy adults, patients with severe HTG, and patients with FCS (NCT03783377)	
Evinacumab	mAb against ANGPTL3	Phase I. SADS in healthy adults with TG 150-450 mg/dl and LDL-C >100 mg/dl (n = 83) (50)	$\label{eq:subcutaneous:} \frac{Subcutaneous:}{TG: -21\% \text{ to } -64\% \text{ (day 4); } -6\% \text{ to } -10\% \text{ (day 15)}} \\ LDL-C: -10\% \text{ to } +1\% \text{ (day 4); } -5\% \text{ to } -17\% \\ (\text{day 15)} \\ \frac{Intravenous:}{TG: -71\% \text{ to } -80\% \text{ (day 4); } -31\% \text{ to } -50\% \\ (\text{day 15)} \\ LDL-C: -15\% \text{ to } -24\% \text{ (day 4); } -12\% \text{ to } -23\% \\ (\text{day 15)} \\ HDL-C: -9\% \text{ to } -16\% \text{ (day 4); } -16\% \text{ to } -25\% \\ (\text{day 15)} \\ Safety: \text{ No SAE reported} \\ \hline \end{tabular}$	Phase II study ongoing in patients with persistent HC despite maximally tolerated lipid-lowering therapy (NCT03175367)	
		Phase I. Patients with TG > 150 and \leq 450 mg/dl and LDL-C \geq 100 mg/dl; SADS (<i>n</i> = 83) and MADS (<i>n</i> = 56) (51)	SADS: TG: -55% (250 mg SC) and -88% (10 mg/kg IV) (day 4) LDL-C: -21% (250 mg SC) and -23% (10 mg/kg IV) (day 8) MADS: TG: -50% (450 mg/wk SC) and -88% (20 mg/kg every 4 wk IV) (day 15) LDL-C: -22% (300 mg/wk SC) and -25.1% (20 mg/kg every 4 wk IV) (day 57) Safety: Drug well tolerated with no SAE or drug discontinuation		

Table 1 (Continued)

Drug	Mechanism	Clinical trial stage, patient population, reference	Results	Status/future directions
AKCEA- ANGPTL3- L _{Rx}	ASO targeting ANGPTL3ª	Phase I. Healthy adults with LDL-C >70 mg/dl and TG >90 mg/dl (n = 32); MADS (weekly dosing) (52)	ANGPTL3: -47% (10 mg); -72% (20 mg); -81% (40 mg); -84% (60 mg) TG: -33% (10 mg); -63% (20 mg); -54% (40 mg); -50% (60 mg) LDL-C: -1% (10 mg); -4% (20 mg); -25% (40 mg); -39% (60 mg) Safety: No bleeding episodes or significant decreases in platelets; no SAE reported	Phase II study ongoing in patients with DM, HTG, and NAFLD (NCT03455777)
ARO-ANG3	siRNA targeting ANGPTL3 ^a	Phase I. SADS in healthy adults with TG >100 mg/dl and LDL-C >70 mg/dl (n = 40) (53)	<u>Mean max reduction:</u> <u>ANGPTL3:</u> -55% (35 mg) to -83% (300 mg) TG: -31% (35 mg) to -66% (300 mg) LDL-C: -9% (35 mg) to -30% (300 mg) HDL-C: -8% (35 mg) to -26% (300 mg) Reductions maintained at wk 16 <u>Safety</u> : 1 ISR; no SAE reported	Phase I ongoing in healthy adults and patients with FH or HTG (NCT03747224)
TQJ230 (formerly AKCEA- APO(a)- L _{Rx}	ASO targeting Lp(a)	Phase II. Patients with ASCVD and Lp(a) >60 mg/dl; MADS (n = 286) (54)	<i>Lp(a):</i> -35% (20 mg every 4 wk); -56% (40 mg every 4 wk); -58% (20 mg every 2 wk); -72% (60 mg every 4 wk); -80% (20 mg every wk) at 6 mo <i>Safety:</i> More ISR with drug versus placebo; no SAE reported	Phase III CVOT ongoing in patients with ASCVD and Lp(a) ≥70 mg/dl (NCT04023552)
AMG890	siRNA targeting Lp(a)	Preclinical studies. Cynomolgus monkeys (55)	<i>Lp(a)</i> : -85% to -90% (3 mg/kg weekly for 3 wk); reductions maintained up to 60 days	Phase I SADS completed in patients with elevated Lp(a) (n = 80) to evaluate safety (NCT03626662) Phase II dosing study ongoing in patients with ASCVD and Lp(a) >150 nmol/L $(n = 240)$ to evaluate percent change in Lp(a) (NCT04270760)

^aGalNAc conjugated.

Abbreviations: ANGPTL3, angiopoietin-like protein 3; apo, apolipoprotein; ASO, antisense oligonucleotide; ASCVD, atherosclerotic cardiovascular disease; CVOT, cardiovascular outcomes trial; DM, diabetes mellitus; EMA, European Medicines Agency; FCS, familial chylomicronemia syndrome; FDA, US Food and Drug Administration; FH, familial hypercholesterolemia; HC, hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; HTG, hypertriglyceridemia; ISR, injection-site reaction; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); mAb, monoclonal antibody; MADS, multiple-ascending dose study; NAFLD, nonalcoholic fatty liver disease; mo, month or months; SADS, single-ascending dose study; SAE, serious adverse events; SC, subcutaneous; siRNA, small interfering ribonucleic acid; TG, triglycerides; wk, week or weeks; yr, year.

Angiopoietin-like Protein 3 Inhibition

Strategies to inhibit ANGPTL3 include mAb and RNA interference therapies (**Table 1**). Evinacumab (REGN1500) is the first-in-class mAb against ANGPTL3 that has effected profound reductions in TG and LDL-C in early-phase clinical trials (50, 51). Results of a double-blind randomized placebo-controlled clinical trial in 60 patients with HoFH showed that patients receiving evinacumab demonstrated relative reduction in LDL-C of 49% compared with placebo, and no serious adverse events were reported (56). Both AKCEA-ANGPTL3- L_{Rx} (a GalNAc-conjugated ASO) and ARO-ANG3 (GalNAc-modified siRNA) target production of ANGPTL3 and have been tested in phase I trials (**Table 1**) (52, 53).

NEW THERAPIES TARGETING LIPOPROTEIN(A)

Genetic, epidemiological, and clinical studies have established that elevated concentrations of lipoprotein(a) are associated with increased risk for coronary heart disease. Lipoprotein(a) has a pleiotropic effect on atherosclerosis: It is proatherogenic owing to its LDL moiety, prothrombotic owing to the homology of apo(a) with plasminogen, and carries oxidized phospholipids (57), which mediate arterial wall inflammation. Targeting lipoprotein(a) may therefore be of incremental value beyond lowering LDL-C, even in individuals without elevated LDL-C (58).

PCSK9 Inhibitors

Evolocumab and alirocumab have been shown to reduce lipoprotein(a) levels by 23–27% (4, 5). Furthermore, patients with higher baseline lipoprotein(a) levels had greater absolute lipoprotein(a) reduction and greater absolute risk reduction for cardiovascular events (59, 60). In a subgroup analysis of ODYSSEY OUTCOMES, alirocumab-induced lipoprotein(a) reduction independently contributed to reduction in risk of cardiovascular events, beyond LDL-C or non-HDL-C lowering (59).

APO(a)-L_{Rx}

 $APO(a)-L_{Rx}$ is a GalNAc-conjugated second-generation ASO that targets and reduces the synthesis of apo(a) in the liver. It demonstrated dose-dependent and sustained reduction in lipoprotein(a) levels by up to 80% in a phase II clinical trial. The ASO was well tolerated, but injection-site erythema was reported more often in those receiving drug compared with placebo (54).

AMG 890

AMG 890 (formerly ARO-LPA) is a GalNAc-conjugated siRNA designed to inhibit lipoprotein(a) production. A phase I randomized double-blind placebo-controlled single-ascending dose clinical trial to evaluate the safety, pharmacokinetics, and pharmacodynamics of AMG 890 in 80 subjects with elevated lipoprotein(a) has been completed (NCT03626662). A phase II double-blind randomized placebo-controlled clinical trial in 240 patients with elevated lipoprotein(a) is in progress (NCT04270760).

NEW APPROACHES TO INFLAMMATION

Atherosclerosis is an inflammatory process, and the immune system plays an important role in both initiation and progression of the disease. Atherosclerosis is characterized by cholesterolrich atheromas, which begin with subendothelial infiltration and retention of apo B–containing lipoproteins. Endothelial dysfunction characterized by increased expression of adhesion molecules enhances adhesion and migration of monocytes and lymphocytes, which in turn secrete cytokines, chemokines, and growth factors, leading to migration and proliferation of smooth muscle cells and eventually resulting in complex atherosclerotic lesions. Increased levels of LDL and postprandial TG-rich lipoproteins also lead to development of foamy monocytes in the circulation, which have increased expression of CD11c and increased adhesion to endothelium with subsequent transmigration to become foamy macrophages (61, 62).

Anti-inflammatory Therapies with Cardiovascular Outcomes Trials

Although Anitschkow & Chalatow (63) reported foamy monocytes in atherosclerosis at the beginning of the twentieth century, and Virchow (64) described atherosclerosis as an inflammatory disorder in the mid-nineteenth century, numerous clinical trials evaluating the use of antiinflammatory or immune-modulating treatments, such as oxidized LDL antibody, darapladib (an Lp-PLA2 inhibitor), varespladib (a secretory phospholipase A2 inhibitor), atreleuton (a 5lipoxygenase inhibitor), and losmapimod (a p38 mitogen–activated protein kinase inhibitor), failed to show any beneficial effect on ASCVD events. In this section, we first discuss the most recent clinical trials evaluating the use of anti-inflammatory agents for ASCVD risk reduction and then summarize anti-inflammatory therapies in clinical development.

Canakinumab. Canakinumab is a mAb against interleukin (IL)–1 β . In CANTOS, a phase III randomized placebo-controlled clinical trial in 10,061 participants with a history of MI and hsCRP levels >2.0 mg/L, canakinumab 150 mg resulted in a 15% reduction in the primary composite endpoint of MI, stroke, and cardiovascular death [hazard ratio (HR) 0.85,95% confidence interval (CI) 0.74–0.98] compared with placebo (9). Key secondary endpoints, including MI, unstable angina requiring urgent revascularization, and any coronary revascularizations, were also reduced. There was no significant reduction in cardiovascular mortality or stroke. CANTOS was a landmark trial because it was the first to show that a therapy specifically targeting inflammation provided clinical benefit independent of lowering lipoproteins. Although canakinumab therapy was associated with increased risk for fatal infection, it was also associated with reduced risk for death from cancer, with a reduction in lung cancer. Furthermore, participants who achieved hsCRP levels <2 mg/L after a single dose of canakinumab had greater reduction in cardiovascular outcomes (by 25%) and all-cause mortality (by 31%) (65). These findings have important clinical implications, as they may help identify a subset of patients in whom canakinumab or other anti-inflammatory therapy may prove particularly clinically effective.

Beyond residual cholesterol risk, these results support the concept of residual inflammatory risk. Residual inflammatory risk is not uncommon; in both the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) (66) and IMPROVE-IT (3) trials, almost one-third of statin-treated patients had hsCRP >2 mg/L. More than one-third of the patients in the PCSK9 mAb cardiovascular outcomes trials met the eligibility criteria for CANTOS despite achieving very low LDL-C (15).

Methotrexate. CANTOS was followed by the Cardiovascular Inflammation Reduction (CIRT) trial, which evaluated the clinical efficacy of methotrexate in 4,786 patients with prior MI or multivessel coronary disease (with either diabetes or metabolic syndrome). Low-dose methotrexate (5–20 mg) did not significantly reduce the composite endpoint of nonfatal MI, stroke, or cardiovascular death (HR 1.01, 95% CI 0.82–1.25), and the trial was stopped early for futility after a median follow-up of 2.3 years (67). Compared with CANTOS, CIRT had two major limitations that may have contributed to its negative results: First, many patients had only modest levels of inflammation (median hsCRP 1.6 mg/L), and second, methotrexate, a nonspecific approach to immunomodulation, was not associated with significantly reduced key inflammatory parameters such as hsCRP, IL-1β, or IL-6.

Colchicine. Colchicine acts by preventing cytoskeletal microtubule formation through inhibition of tubulin polymer assembly. It is an anti-inflammatory medication used to treat gouty arthritis and pericarditis. In a prospective randomized open-label clinical trial in 532 patients with stable coronary artery disease, colchicine 0.5 mg/day significantly reduced risk for the primary cardiovascular endpoint (acute coronary syndrome, out-of-hospital cardiac arrest, or ischemic stroke) compared with no colchicine; the reduction was driven primarily by reduction in acute coronary syndrome events (68).

In the recent Colchicine Cardiovascular Outcomes Trial (COLCOT), a larger randomized double-blind placebo-controlled trial in 4,745 patients with recent MI (<30 days), addition of colchicine was associated with a significant 23% reduction in the primary endpoint (composite of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent coronary revascularization) compared with placebo over median 22.6-month follow-up (69). Each component of the primary endpoint was significantly reduced, with marked benefit for stroke. Diarrhea and pneumonia were more common with colchicine than with placebo.

COLCOT is the first clinical trial to show a role for an anti-inflammatory agent in ASCVD risk reduction in the acute post-MI period. The ongoing Colchicine and Spironolactone in Patients with MI/SYNERGY Stent Registry (CLEAR SYNERGY) trial is evaluating the long-term effects of colchicine in patients with recent ST elevation myocardial infarction to try to confirm these findings (NCT03048825).

Drug	Mechanism	Clinical trial stage, patient population, reference	
Anakinra	IL-1 receptor	Phase II. Patients with NSTEMI ($n = 182$); significant reduction in hsCRP and IL-6	
	antagonist	levels over 14 days (71)	
		Phase II/III. Patients with STEMI ($n = 124$); primary endpoint: change in hsCRP levels	
		(NCT01950299; ongoing)	
Tocilizumab	Anti-IL-6	Phase II. NSTEMI patients ($n = 117$); significantly lower hsCRP and troponin (72)	
	receptor	Phase II. STEMI patients ($n = 200$); primary endpoint: acute-phase myocardial salvage	
	antibody	index assessed by cardiac magnetic resonance imaging (NCT03004703; ongoing)	
Hydroxychloroquine	Multiple	Observational studies. RA and SLE patients on hydroxychloroquine with significantly	
	mecha-	lower incidence of cardiovascular events	
	nisms	Phase IV. CAD patients ($n \approx 90$); primary endpoint: change in hsCRP (NCT02874287;	
		ongoing)	
		Phase IV. NSTEMI patients ($n = 124$); primary endpoint: cardiovascular outcomes	
		(NCT02648464; ongoing)	
Xilonix	Anti-IL-1α	Phase II. Post-PTCA patients ($n = 43$); nonsignificant trend toward improved vessel	
	antibody	patency, well tolerated (73)	
IL-2 (low dose)	Promotion of	Phase I/II. Patients with stable CAD ($n = 25$) and patients with acute coronary syndrome	
	Tregs	(n = 32); primary endpoints: safety and tolerability, change in circulating Tregs (74)	
Ziltivekimab	Anti–IL-6	Phase I/Ib and phase I/II. Patients with CKD on dialysis; hsCRP and serum amyloid A	
	ligand	significantly reduced, trend toward improved NT-proBNP (NCT03126318,	
	monoclonal	NCT02868229)	
	antibody	Phase IIb. Patients with CKD; primary endpoint: hsCRP reduction (NCT03926117;	
		completed)	

Table 2 Anti-inflammatory therapies for cardiovascular risk reduction in development

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; NSTEMI, non–ST-segment elevation myocardial infarction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PTCA, percutaneous transluminal coronary angioplasty; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; STEMI, ST-segment elevation myocardial infarction; Tregs, regulatory T cells.

Anti-inflammatory Drugs in Development

Several promising anti-inflammatory therapies are in different phases of clinical trials (70). **Table 2** lists some of the targeted therapies with their pathways and stage of development.

CONCLUSION

Although statins remain the first-line lipid therapy for ASCVD prevention, residual ASCVD risk despite guideline-recommended statin use emphasizes the need for additional therapies. Recently approved and emerging agents offer options for further LDL-C reductions, in combination with statin or as monotherapy, as well as alternative targets including TG and TG-rich lipoproteins, lipoprotein(a), and inflammation (see **Figure 1**). The clinical utility of these agents is the subject of recently completed and ongoing clinical trials, including essential outcomes studies, to evaluate their potential for risk reduction in clinical practice.

DISCLOSURE STATEMENT

Christie M. Ballantyne has received grant/research support through his institution from Abbott Diagnostics, Akcea, Amgen, Esperion, Novartis, Regeneron, and Roche Diagnostic and is a consultant for Abbott Diagnostics, Akcea, Althera, Amarin, Amgen, Arrowhead, AstraZeneca, Corvidia, Denka Seiken, Esperion, Gilead, Janssen, Matinas BioPharma Inc., New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo.

LITERATURE CITED

- 1. Baigent C, Keech A, Kearney PM, et al. 2005. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 366:1267–78
- 2. Baigent C, Blackwell L, Emberson J, et al. 2010. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 376:1670–81
- Cannon CP, Blazing MA, Giugliano RP, et al. 2015. Ezetimibe added to statin therapy after acute coronary syndromes. N. Engl. J. Med. 372:2387–97
- 4. Sabatine MS, Giugliano RP, Keech AC, et al. 2017. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N. Engl. J. Med.* 376:1713–22
- Schwartz GG, Steg PG, Szarek M, et al. 2018. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N. Engl. J. Med. 379:2097–107
- Grundy SM, Stone NJ, Bailey AL, et al. 2019. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *7. Am. Coll. Cardiol.* 73:3168–209
- Mach F, Baigent C, Catapano AL, et al. 2020. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur. Heart J.* 41:111–88
- 8. Bhatt DL, Steg PG, Miller M, et al. 2019. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *J. Am. Coll. Cardiol.* 73:2791–802
- 9. Ridker PM, Everett BM, Thuren T, et al. 2017. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N. Engl. J. Med. 377:1119–31
- Dicembrini I, Giannini S, Ragghianti B, et al. 2019. Effects of PCSK9 inhibitors on LDL cholesterol, cardiovascular morbidity and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials. *J. Endocrinol. Investig.* 42:1029–39
- 11. Giugliano RP, Pedersen TR, Park JG, et al. 2017. Clinical efficacy and safety of achieving very low LDLcholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet* 390:1962–71

- Murphy SA, Pedersen TR, Gaciong ZA, et al. 2019. Effect of the PCSK9 inhibitor evolocumab on total cardiovascular events in patients with cardiovascular disease: a prespecified analysis from the FOURIER trial. *JAMA Cardiol.* 4:613–19
- 13. Bonaca MP, Nault P, Giugliano RP, et al. 2018. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease. *Circulation* 137:338–50
- 14. Sabatine MS, De Ferrari GM, Giugliano RP, et al. 2018. Clinical benefit of evolocumab by severity and extent of coronary artery disease. *Circulation* 138:756–66
- Bohula EA, Giugliano RP, Leiter LA, et al. 2018. Inflammatory and cholesterol risk in the FOURIER trial. *Circulation* 138:131–40
- Marston NA, Kamanu FK, Nordio F, et al. 2020. Predicting benefit from evolocumab therapy in patients with atherosclerotic disease using a genetic risk score: results from the FOURIER trial. *Circulation* 141:616–23
- Roe MT, Li QH, Bhatt DL, et al. 2019. Risk categorization using new American College of Cardiology/ American Heart Association guidelines for cholesterol management and its relation to alirocumab treatment following acute coronary syndromes. *Circulation* 140:1578–89
- Goodman SG, Aylward PE, Szarek M, et al. 2019. Effects of alirocumab on cardiovascular events after coronary bypass surgery. J. Am. Coll. Cardiol. 74:1177–86
- Jukema JW, Szarek M, Zijlstra LE, et al. 2019. Alirocumab in patients with polyvascular disease and recent acute coronary syndrome: ODYSSEY Outcomes Trial. J. Am. Coll. Cardiol. 74:1167–76
- Koskinas KC, Windecker S, Pedrazzini G, et al. 2019. Evolocumab for early reduction of LDL cholesterol levels in patients with acute coronary syndromes (EVOPACS). J. Am. Coll. Cardiol. 74:2452–62
- Santos RD, Stein EA, Hovingh GK, et al. 2020. Long-term evolocumab in patients with familial hypercholesterolemia. *J. Am. Coll. Cardiol.* 75:565–74
- 22. Koren MJ, Sabatine MS, Giugliano RP, et al. 2019. Long-term efficacy and safety of evolocumab in patients with hypercholesterolemia. *J. Am. Coll. Cardiol.* 74:2132–46
- Pinkosky SL, Newton RS, Day EA, et al. 2016. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat. Commun.* 7:13457
- Ray KK, Bays HE, Catapano AL, et al. 2019. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N. Engl. J. Med. 380:1022–32
- Ballantyne CM, Laufs U, Ray KK, et al. 2019. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur. J. Prev. Cardiol.* 27:593–603
- Ray KK, Stoekenbroek RM, Kallend D, et al. 2018. Effect of an siRNA therapeutic targeting PCSK9 on atherogenic lipoproteins. *Circulation* 138:1304–16
- Nair JK, Willoughby JL, Chan A, et al. 2014. Multivalent N-acetylgalactosamine-conjugated siRNA localizes in hepatocytes and elicits robust RNAi-mediated gene silencing. *J. Am. Chem. Soc.* 136:16958–61
- Ray KK, Wright RS, Kallend D, et al. 2020. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N. Engl. J. Med. 382:1507–19
- 29. Raal FJ, Kallend D, Ray KK, et al. 2020. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N. Engl. J. Med. 382:1520–30
- Ray KK, Stoekenbroek RM, Kallend D, et al. 2019. Effect of 1 or 2 doses of inclisiran on low-density lipoprotein cholesterol levels: one-year follow-up of the ORION-1 randomized clinical trial. *JAMA Cardiol.* 4:1067–75
- Bhatt DL, Steg PG, Miller M, et al. 2019. Effects of icosapent ethyl on total ischemic events: from REDUCE-IT. J. Am. Coll. Cardiol. 73:2791–802
- 32. Am. Diabetes Assoc. 2020. Cardiovascular disease and risk management: standards of medical care in diabetes—2020. *Diabetes Care* 43(Suppl. 1):S111–34
- Orringer CE, Jacobson TA, Maki KC. 2019. National Lipid Association scientific statement on the use of icosapent ethyl in statin-treated patients with elevated triglycerides and high or very-high ASCVD risk. *J. Clin. Lipidol.* 13:860–72
- Kastelein JJP, Stroes ESG. 2019. FISHing for the miracle of eicosapentaenoic acid. N. Engl. J. Med. 380:89–90

- Wu H, Xu L, Ballantyne CM. 2020. Dietary and pharmacological fatty acids and cardiovascular health. *J. Clin. Endocrinol. Metab.* 105:1030–45
- Bays HE, Ballantyne CM, Braeckman RA, et al. 2013. 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* 13:37–46
- 37. Miller M, Ballantyne CM, Bays HE, et al. 2019. Effects of icosapent ethyl (eicosapentaenoic acid ethyl ester) on atherogenic lipid/lipoprotein, apolipoprotein, and inflammatory parameters in patients with elevated high-sensitivity C-reactive protein (from the ANCHOR Study). Am. J. Cardiol. 124:696–701
- Kohli P, Levy BD. 2009. Resolvins and protectins: mediating solutions to inflammation. Br. J. Pharmacol. 158:960–71
- 39. Nishio R, Shinke T, Otake H, et al. 2014. Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma. *Atherosclerosis* 234:114–19
- 40. Budoff M. 2019. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: The EVAPORATE study. Abstract presented at American Heart Association Scientific Sessions, Nov. 18, Philadelphia, PA
- Ginsberg HN, Elam MB, Lovato LC, et al. 2010. Effects of combination lipid therapy in type 2 diabetes mellitus. N. Engl. J. Med. 362:1563–74
- 42. Scott R, O'Brien R, Fulcher G, et al. 2009. 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* 32:493–98
- 43. Ida S, Kaneko R, Murata K. 2019. Efficacy and safety of pemafibrate administration in patients with dyslipidemia: a systematic review and meta-analysis. *Cardiovasc. Diabetol.* 18:38
- Stitziel NO, Khera AV, Wang X, et al. 2017. ANGPTL3 deficiency and protection against coronary artery disease. *J. Am. Coll. Cardiol.* 69:2054–63
- 45. Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjaerg-Hansen A. 2014. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *N. Engl. J. Med.* 371:32–41
- Witztum JL, Gaudet D, Freedman SD, et al. 2019. Volanesorsen and triglyceride levels in familial chylomicronemia syndrome. N. Engl. 7. Med. 381:531–42
- European Medicines Agency. 2019. First treatment for rare disease characterised by high levels of trighycerides in blood. Press Release, Jan. 3. https://www.ema.europa.eu/en/news/first-treatment-rare-diseasecharacterised-high-levels-trighycerides-blood
- Alexander VJ, Xia S, Hurh E, et al. 2019. N-acetyl galactosamine-conjugated antisense drug to APOC3 mRNA, triglycerides and atherogenic lipoprotein levels. *Eur. Heart J.* 40:2785–96
- Ballantyne CM. 2019. RNA interference targeting apolipoprotein C-III results in deep and prolonged reductions in plasma triglycerides. Abstract presented at American Heart Association Scientific Sessions, Nov. 18, Philadelphia, PA
- 50. Dewey FE, Gusarova V, Dunbar RL, et al. 2017. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N. Engl. J. Med.* 377:211–21
- Ahmad Z, Banerjee P, Hamon S, et al. 2019. Inhibition of angiopoietin-like protein 3 with a monoclonal antibody reduces triglycerides in hypertriglyceridemia. *Circulation* 140:470–86
- Graham MJ, Lee RG, Brandt TA, et al. 2017. Cardiovascular and metabolic effects of ANGPTL3 antisense oligonucleotides. N. Engl. J. Med. 377:222–32
- 53. Watts GF. 2019. RNA interference targeting bepatic angiopoietin-like protein 3 results in prolonged reductions in plasma triglycerides and LDL-C in human subjects. Abstract presented at American Heart Association Scientific Sessions, Nov. 18, Philadelphia, PA
- 54. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, et al. 2020. Lipoprotein(a) reduction in persons with cardiovascular disease. *N. Engl. J. Med.* 382:244–55
- 55. Melquist S. 2016. *Targeting apolipoprotein(a) with a novel RNAi delivery platform as a prophylactic treatment to reduce risk of cardiovascular events in individuals with elevated lipoprotein(a)*. Abstract presented at American Heart Association Scientific Sessions, Nov. 14, New Orleans, LA
- 56. Raal F. 2020. *Evinacumab in patients with homozygous familial hypercholesterolemia*. Abstract presented at American College of Cardiology Scientific Sessions, Apr. 30, virtual

- 57. Bergmark C, Dewan A, Orsoni A, et al. 2008. A novel function of lipoprotein [a] as a preferential carrier of oxidized phospholipids in human plasma. *J. Lipid Res.* 49:2230–39
- 58. Khera AV, Everett BM, Caulfield MP, et al. 2014. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *Circulation* 129:635–42
- 59. Bittner VA, Szarek M, Aylward PE, et al. 2020. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. *J. Am. Coll. Cardiol.* 75:133–44
- O'Donoghue ML, Fazio S, Giugliano RP, et al. 2019. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. *Circulation* 139:1483–92
- Wu H, Gower RM, Wang H, et al. 2009. Functional role of CD11c⁺ monocytes in atherogenesis associated with hypercholesterolemia. *Circulation* 119:2708–17
- Gower RM, Wu H, Foster GA, et al. 2011. CD11c/CD18 expression is upregulated on blood monocytes during hypertriglyceridemia and enhances adhesion to vascular cell adhesion molecule-1. Arterioscler: Thromb. Vasc. Biol. 31:160–66
- Anitschkow N, Chalatow S. 1913. Über experimentelle Cholesterinsteatose und ihre Bedeutung f
 ür die Entstehung einiger pathologischer Prozesse. Zentrbl. Allg. Pathol. Pathol. Anat. 24:1–9
- Virchow R. 1858. Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelebre. Berlin: August Hirschwald.
- 65. Ridker PM, MacFadyen JG, Everett BM, et al. 2018. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet* 391:319–28
- Cannon CP, Braunwald E, McCabe CH, et al. 2004. Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes. N. Engl. J. Med. 350:1495–504
- Ridker PM, Everett BM, Pradhan A, et al. 2019. Low-dose methotrexate for the prevention of atherosclerotic events. N. Engl. J. Med. 380:752–62
- Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. 2013. Low-dose colchicine for secondary prevention of cardiovascular disease. *J. Am. Coll. Cardiol.* 61:404–10
- Tardif JC, Kouz S, Waters DD, et al. 2019. Efficacy and safety of low-dose colchicine after myocardial infarction. N. Engl. J. Med. 381:2497–505
- Aday AW, Ridker PM. 2019. Targeting residual inflammatory risk: a shifting paradigm for atherosclerotic disease. Front. Cardiovasc. Med. 6:16
- Morton AC, Rothman AM, Greenwood JP, et al. 2015. The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. *Eur. Heart J.* 36:377–84
- 72. Kleveland O, Kunszt G, Bratlie M, et al. 2016. Effect of a single dose of the interleukin-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with non-ST-elevation myocardial infarction: a double-blind, randomized, placebo-controlled phase 2 trial. *Eur. Heart J.* 37:2406–13
- El Sayed H, Kerensky R, Stecher M, et al. 2016. A randomized phase II study of Xilonix, a targeted therapy against interleukin 1α, for the prevention of superficial femoral artery restenosis after percutaneous revascularization. *J. Vasc. Surg.* 63:133–41.e1
- 74. Zhao TX, Kostapanos M, Griffiths C, et al. 2018. Low-dose interleukin-2 in patients with stable ischaemic heart disease and acute coronary syndromes (LILACS): protocol and study rationale for a randomised, double-blind, placebo-controlled, phase I/II clinical trial. *BMJ Open* 8:e022452