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REVIEW

Current pharmacotherapies for atherosclerotic cardiovascular diseases

Jong-Gil Park[1] · **Goo Taeg Oh**[2]

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Abstract Despite the introduction of statins for lowering LDL-C level, atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of death and morbidity worldwide. Combination therapies with statin and other lipid-lowering drugs, including ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, have unlocked additive benefits for treatment of ASCVD, but morbidity and mortality due to ASCVD remain high. New anti-inflammatory therapies have emerged for treatment and prevention of ASCVD to address these problems. Canakinumab neutralization of interleukin-1β (IL-1β) is the only verified therapy, and low-dose methotrexate holds promise due to its efficacy and safety for treatment of ASCVD. However, many agonistic and antagonistic candidates within inflammation pathways have failed to develop into useful drugs for ASCVD because of the complexity of the inflammatory process in atherosclerosis. In this review, we outline current and future pharmaceutical therapies for ASCVD in terms of lipid-modifying strategies and anti-inflammation treatments.

Keywords Atherosclerotic cardiovascular diseases (ASCVD) · Pharmaceutical therapies · Lipid-lowering drugs · Anti-inflammatory therapies · Statin · Ezetimibe · PCSK9 inhibitor · Canakinumab · Methotrexate

✉ Goo Taeg Oh
gootaeg@ewha.ac.kr

[1] Biotherapeutics Translational Research Center, Korea Research Institute of Bioscience & Biotechnology (KRIBB), 125 Gwahak-ro, Yuseong-gu, Daejeon 34141, Republic of Korea

[2] Immune and Vascular Cell Network Research Center, National Creative Initiatives, Department of Life Sciences, Ewha Womans University, 52 Ewhayeodae-gil, Seodaemun-gu, Seoul 120-750, Republic of Korea

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of death and morbidity worldwide, despite the introduction of statins about 30 years ago (Benjamin et al. 2018). The pathogenesis of atherosclerosis is initiated by endothelial dysfunction and structural alterations of arterial walls triggered by disturbed laminar stress and elevated circulating apolipoprotein B (apoB)-containing lipoprotein, mainly low-density lipoprotein (LDL) (Kwon et al. 2008; Moore and Tabas 2011). Exposure of subendothelial proteoglycans caused by structural alterations of the aorta leads to accumulation of LDL under the endothelial layer through binding with apoB (Kwon et al. 2008). LDL particles in the intima are readily modified by reactive oxygen species, which trigger expression of adhesion molecules and release of chemokines on endothelial cells, leading to recruitment of immune cells in the intima (Weber and Noels 2011). Macrophages retained in the intima engulf modified LDLs such as oxidized LDL (oxLDL) through scavenger receptors, which drive the transformation of macrophages into foam cells (Sakakura et al. 2013). In addition to foam cell formation, macrophages express various costimulatory molecules that activate other immune cells to create inflammatory conditions in lesions (Weber and Noels 2011). In the process of atheroma propagation, accumulation of apoptotic cells, debris, and cholesterol crystals contributes to development of the necrotic core and in turn to plaque destabilization, leading to plaque rupture or erosion (Ylä-Herttuala et al. 2011). Occlusive thrombosis formed by plaque rupture or

erosion causes acute cardiovascular events, which underlie mortality due to ASCVD (Sakakura et al. 2013). Rupture-prone plaques consist of large necrotic cores with thin fibrous caps, plaque hemorrhages, neovascularization, and adventitial inflammation (Ylä-Herttuala et al. 2011).

Given the pathophysiology of atherosclerosis (Fig. 1), current therapeutic targets and drugs for ASCVD emphasize normalization of plasma lipids including LDL-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) and attenuation of inflammation in lesions (Weber and Noels 2011; Shapiro and Fazio 2016). In this review, we describe and discuss current and future pharmaceutical therapies for ASCVD in terms of lipid-modifying strategies and anti-inflammation treatments.

Lipid-modifying therapies

Risk factors for ASCVD include dyslipidemia, hypertension, diabetes, cigarette smoking, and genetic mutations (Bergheanu et al. 2017; Jellinger et al. 2017) (Fig. 2). Among these, hypercholesterolemia is considered a major risk factor for ASCVD (Nelson 2013). Clinical and experimental data have shown that plasma cholesterol, especially LDL-C, is the catalyst for development of ASCVD (Pedersen et al. 1994; Finking and Hanke 1997). Statin mega-trials based on 26 randomized trials of statins indicate that major ASCVD events and mortality are reduced by 22% and 10%, respectively, after reduction of 39 mg/dL in LDL-C level (Cholesterol Treatment Trialists' et al. 2010). In addition, HDL-C level, hypertriglyceridemia, and lipoprotein(a) (Lp(a)) are considered independent risk factors for ASCVD (Rubin et al. 1991; Elam et al. 2000; Kronenberg and Utermann 2013; Catapano et al. 2017; Jellinger et al. 2017). Although low levels of HDL-C are well correlated with ASCVD, high levels of HDL-C are not related to atheroprotection, indicating that functional HDL level is important (Catapano et al. 2017). Hypertriglyceridemia is a traditional risk factor for ASCVD, but the benefits associated with lower levels of TG in patients with ASCVD are modest (Catapano et al. 2017). Elevated Lp(a), which consists of an LDL-like particle with apolipoprotein A (apoA), has emerged as a risk factor in patients with ASCVD or with strong family history of ASCVD (Kamstrup et al. 2009). In this section, we describe current and future drug therapies and therapeutic targets for regulation of lipid levels in patients with ASCVD (Table 1).

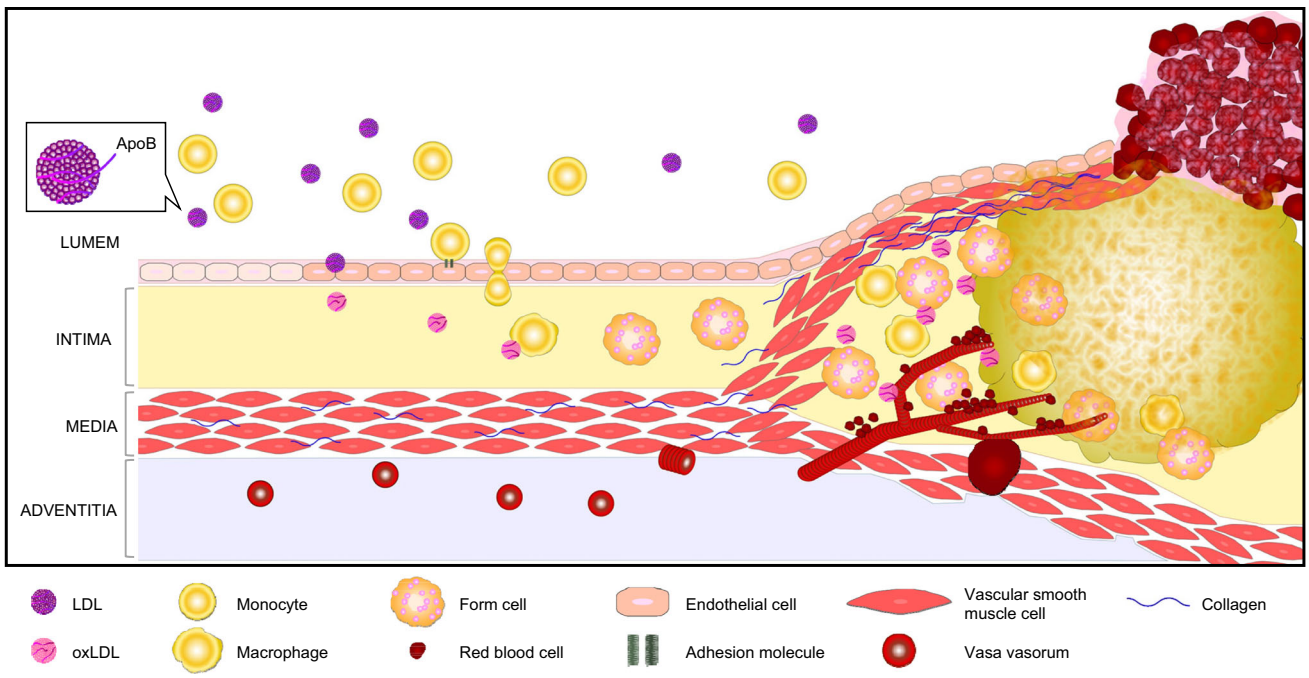

Fig. 1 Pathogenesis of atherosclerosis. Endothelial dysfunction and structural alteration of the arterial wall are triggered by disturbed laminar stress and elevated circulating apoB-containing lipoprotein, leading to accumulation of LDL within the intima. Modified LDL particles in the intima trigger expression of adhesion molecules and release of chemokines on endothelial cells, leading to recruitment of immune cells in the intima. Macrophages retained in the intima engulf modified LDL through scavenger receptors, driving transformation of macrophages into foam cells. Macrophages also express various costimulatory molecules that activate other immune cells, resulting in inflammatory conditions in the lesions. In the process of atheroma propagation, accumulation of apoptotic cells, debris, cholesterol crystals, and intra-plaque hemorrhage lead to development of the necrotic core, contributing to plaque destabilization and leading to plaque rupture or erosion. *ApoB* apolipoptrotein B, *LDL* low-density lipoprotein

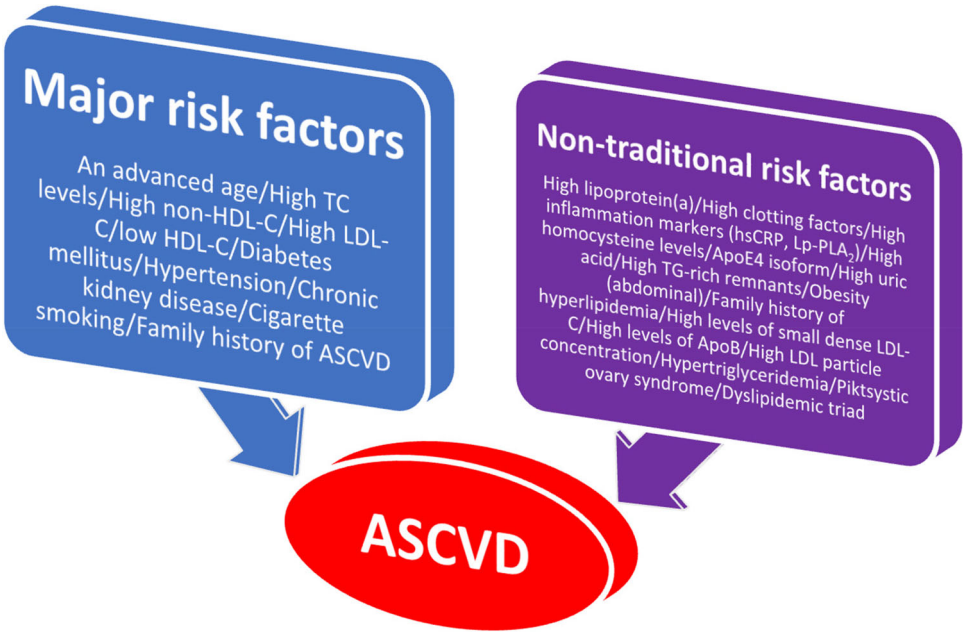

Fig. 2 Risk factors for atherosclerotic cardiovascular disease. *LDL-C* low-density lipoprotein cholesterol, *LDL* low-density lipoprotein, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *ASCVD* atherosclerotic cardiovascular disease, *hsCRP* high-sensitivity C-reactive protein, *Lp-PLA$_2$* lipoprotein-associated phospholipase A$_2$, *ApoE4* apolipoprotein E4, *TG* triglycerides

Statins

After discovery of the first cholesterol-lowering drug, mevastatin (ML-236B), which is produced by the fungus *Penicillium citrinum*, lovastatin (mevinolin, MK803) was derived from the fungus *Aspergillus terreus* and marketed as a cholesterol-lowering drug (Brown et al. 1976). In 1994, the Scandinavian Simvastatin Survival Study (4S) evaluated the cholesterol-lowering effects of simvastatin (20–40 mg/day) on mortality and morbidity in 4444 patients with coronary heart disease (CHD), concluding that simvastatin reduced LDL-C by 35%, total mortality by 30%, and major coronary events by 34% compared to placebo (Pedersen et al. 1994). Follow-up trials have consistently shown that statins effectively reduce morbidity and mortality in high-risk patients with ASCVD and in generally healthy people. The Cholesterol and Recurrent Events (CARE) study determined that administration of pravastatin (40 mg/day) resulted in an absolute decrease of 3% (10.2% in the pravastatin group; 13.2% in the placebo group) in the study end point of frequency of fatal coronary events or nonfatal myocardial infarctions (Sacks et al. 1996). The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study concluded that pravastatin (40 mg/day) treatment resulted in a relative risk reduction of 24% for mortality from CHD as the primary outcome (Long-Term Intervention with Pravastatin in Ischaemic Disease Study 1998). The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) showed that lovastatin (20–40 mg/day) reduced the risk of first acute major coronary events (116 in the lovastatin group; 183 in the placebo group) in generally healthy men and women with average total cholesterol (TC) and LDL-C and below-average HDL-C levels (Downs et al. 1998). Overall, previous trials determined that statins safely reduce morbidity and mortality due to ASCVD, and that 1% reductions of LDL-C produced 1% reductions of ASCVD events, indicating the importance of managing LDL-C level in patients with ASCVD (Cholesterol Treatment Cholesterol Treatment Trialists' (CTT) Collaboration et al. 2010). Statins show potential to lower LDL-C, but residual risks remained high in statin-treated ASCVD patients. Therefore, the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study investigated the optimal level of LDL-C by comparing results of administration of pravastatin (40 mg/day, standard therapy) and atorvastatin (80 mg/day, intensive therapy) (Cannon et al. 2004). The primary end point, which was rate of combined death from ASCVD, was 26.3% in the pravastatin group and 22.4% in the atorvastatin group, indicating a 16% reduction of relative risk after intensive atorvastatin therapy. Mills et al. suggested that intensive statin therapy reduces the risk of non-fatal events but not of CVD deaths in a meta-analysis of randomized clinical trials (Mills et al. 2011). However, they found that intensive statin therapy reduced mortality in patients with acute coronary syndrome.

Collectively, well conducted clinical trials demonstrate that statin therapy produces remarkable results (Table 2), including consistent benefits associated with reduction in rate of ASCVD without major adverse effects. Nevertheless, two-thirds of statin-treated patients with ASCVD experience reoccurrence of CVD events, and some patients

Table 1 Summary of lipid-lowering drugs for treating dyslipidemia

Drugs	Pharmacological mechanism	Medical uses	Adverse effects	Molecules
Statin	Inhibits HMG-Co A reductase Increases expression of LDLR on the surface of hepatocytes Improves endothelial function Modulates inflammatory responses Maintains plaque stability Prevents blood clot formation	Primary prevention for patients with CHD Secondary prevention for people with high risk factors of CHD	Myalgia, arthralgia, elevated transaminases, dyspepsia	Lovastatin Pravastatin Simvastatin Atorvastatin Fluvastatin Rosuvastatin Pitavastatin
Ezetimibe	Decreases cholesterol absorption in the small intestine by blocking the Niemann-Pick C1-like 1 (NPC1L1) protein	Second line therapy for patients who do not tolerate statins or who are unable to achieve target LDL-C	Headache, diarrhea, myalgia, elevated transaminases	Ezetimibe
PCSK9 inhibitor	Humanized monoclonal antibodies bind free plasma PCSK9, preventing LDLR degradation and improving absorption of LDL-C particles by the liver	For patients with heterozygous or homozygous familial hypercholesterolemia with residual LDLR expression	Itching at the injection site, flu-like symptoms	Evolocumab Alirocumab
Bile acid sequestrant	Bile acid sequestrants serve as ion-exchange resins, which sequester bile acids from the enterohepatic circulation, leading to production of more bile acids from cholesterol in the liver	For treatment of hypercholesterolemia and dyslipidemia	Constipation, diarrhea, bloating and flatulence	Cholestyramine Colestipol Colesevelam
Fibrates	Fibrates act as agonists of PPAR-α, which is a master regulator in lipid and lipoprotein metabolism	Accessory therapy in hypercholesterolemia with statins Increases HDL and lowers TG levels Reduces insulin resistance in metabolic syndrome	Mild stomach upset and myopathy, increased risk for gallstones and rhabdomyolysis	Fenofibrate Gemfibrozil Aluminium clofibrate Bezafibrate Ciprofibrate Choline fenofibrate Clinofibrate Clofibrate
Omega-3 polyunsaturated fatty acids	Reduces blood TG and blood pressure, stimulates blood circulation, and increases the breakdown of fibrin	Effective TG-lowering agents, putative benefits including enhanced endothelial function and vasodilation, decreased platelet aggregation, and decreased myocyte excitability	Fishy taste, fishy breath, stomach upset, loose stools, nausea	HTA, ALA, SDA, ETE, ETA, EPA, HPA, DPA, DHA, Tetracosapentaenoic acid, Nisinic acid

HMG-Co A 3-hydroxy-3-methyl-glutaryl-coenzyme A, *LDLR* low-density lipoprotein receptor, CHD coronary heart disease, *LDL-C* low-density lipoprotein cholesterol, *PCSK9* proprotein convertase subtilisin/kexin type 9, *PPAR-α* peroxisome proliferator-activated receptor-α, *HDL* high-density lipoprotein, *HTA* hexadecatrienoic acid, *ALA* α-linolenic acid, *SDA* stearidonic acid, *ETE* eicosatrienoic acid, *ETA* eicosatetraenoic acid, *EPA* eicosapentaenoic acid, *HPA* heneicosapentaenoic acid, *DPA* docosapentaenoic acid, *DHA* docosahexaenoic acid, *Nisinic acid* tetracosa-hexaenoic acid

are unsuitable for statin therapy because of therapeutic intolerance to statins or side effects. Therefore, developing new therapeutic targets and drugs remains critical.

Ezetimibe

Ezetimibe is recommended as second line therapy for patients with statin intolerance or who are unable to reach goal LDL-C level with statin therapy alone (Jellinger et al. 2017). Ezetimibe inhibits dietary cholesterol absorption in the intestine by targeting the Niemann-Pick C1-like 1 (NPC1L1) protein at the jejunal enterocyte brush border (Phan et al. 2012; Cannon et al. 2015). In a meta-analysis of randomized controlled trials, ezetimibe monotherapy significantly changed levels of TC (− 13.46%), LDL-C (− 18.58%), HDL-C (+ 3.00%), and TG (− 8.06%) compared to placebo control (Pandor et al. 2009). In combination therapy with statin, ezetimibe induced incremental reduction of LDL-C by 23–24% (Cannon et al. 2015). Although early ezetimibe/statin combination trials

Table 2 Summary of landmark statin trials

Year	Clinical trial	Study size	Drug/dose/duration	Change in serum lipids	Primary endpoint	Results
1994	4S (Pedersen et al. 1994)	4444 patients with CHD	Simvastatin 20–40 mg/days 5.4 years	TC (− 25%) LDL-C (− 35%) HDL-C (+ 8%) TG (− 10%)	Coronary death	8.5% in the placebo group; 5% in the simvastatin group; RR 0.58, 95% CI 0.46–0.73
1995	WOSCOPS (Shepherd et al. 1995)	6595 males with hypercholesterolemia	Pravastatin 40 mg/days 4.9 years	TC (− 20%) LDL-C (− 26%) HDL-C (+ 5%) TG (− 12%)	Nonfatal MI and death from CHD	7.9% in the placebo group; 5.5% in the pravastatin group; RRR 31%, 95% CI 17–43%
1996	CARE (Sacks et al. 1996)	4159 patients with MI and average TC level	Pravastatin 40 mg/days 5.0 years	TC (− 20%) LDL-C (− 28%) HDL-C (+ 5%) TG (− 14%)	Fatal coronary event or nonfatal MI	13.2% in the placebo group; 10.2% in the pravastatin; RRR 24%, 95% CI 9–36%
1998	AFCAPS/TexCAPS (Downs et al. 1998)	6605 people with average TC level	Lovastatin 20–40 mg/days 5.2 years	TC (− 18%) LDL-C (− 25%) HDL-C (+ 6%) TG (− 15%)	Acute major coronary event	5.5% in the placebo group; 3.5% in the lovastatin group; RR 0.63, 95% CI 0.50–0.79
1998	LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease Study 1998)	9014 patients with CHD	Pravastatin 40 mg/days 6.1 years	TC (− 18%) LDL-C (− 25%) HDL-C (+ 5%) TG (− 11%)	Coronary death	8.3% in the placebo group; 6.4% in the pravastatin; RRR 24%, 95% CI 12–35%
2002	PROSPER (Shepherd et al. 2002)	5804 elderly people with risk factors for CVD	Pravastatin 40 mg/days 3.2 years	LDL-C (− 34%) HDL-C (+ 5%) TG (− 13%)	Combined CVD event	16.2% in the placebo group; 14.1% in the pravastatin group; HR 0.85, 95% CI 0.74–0.97
2003	ASCOT-LLA (Sever et al. 2003)	19,342 hypertensive patients with average TC	Atorvastatin 10 mg/dayss 3.3 years	TC (− 19%) LDL-C (− 29%) HDL-C (+ 0%) TG (− 14%)	Nonfatal MI and fatal CHD	2.99% in the placebo group; 1.93% in the atorvastatin group; HR 0.64, 95% CI 0.50–0.83
2004	CARDS (Colhoun et al. 2004)	2838 type 2 diabetic patients without high LDL-C	Atorvastatin 10 mg/days 3.9 years	TC (− 26%) LDL-C (− 40%) HDL-C (+ 1%) TG (− 19%)	Occurrence of a first major CVD event	9.0% in the placebo group; 5.8% in the atorvastatin group; RR 37%, 95% CI − 52 to − 17

Table 2 continued

Year	Clinical trial	Study size	Drug/dose/duration	Change in serum lipids	Primary endpoint	Results
2004	PROVE IT-TIMI 22 (Cannon et al. 2004)	4162 patients with acute coronary syndrome	Standard therapy Pravastatin 40 mg/days 2.0 years	LDL-C (− 22%) HDL-C (+ 8.1%)	Combined death, MI, unstable angina, revascularization, and stroke	26.3% in the pravastatin group; 22.4% in the atorvastatin group; RHR 16%, 95% CI 5–26%
			Intensive therapy Atorvastatin 80 mg/days 2.0 years	LDL-C (− 51%) HDL-C (+ 6.5%)		
2006	ASTEROID (Chhatriwalla et al. 2006)	349 patients who received intensive statin treatment with serial IVUS examinations	Intensive therapy Rosuvastatin 40 mg/days 2.0 years	TC (− 33.8%) LDL-C (− 53.2%) HDL-C (+ 14.7%) TG (− 14.5%)	Change in PAV by IVUS	− 0.79% (97.5% CI − 12.1% to − 0.53%) after rosuvastatin treatment
2008	JUPITER (Ridker et al. 2008)	17,802 healthy people with average LDL-C and high hsCRP	Rosuvastatin 20 mg/days 1.9 years	hsCRP (− 37%) LDL-C (− 50%) HDL-C (+ 4%) TG (− 17%)	Occurrence of a first major CVD event	2.8% in the placebo group; 1.5% in the rosuvastatin group; HR 0.56, 95% CI 0.46–0.69
2011	SATURN (Nicholls et al. 2011)	1039 patients with coronary disease	Intensive therapy Atorvastatin 80 mg/days 2.0 years	TC (− 25.5%) LDL-C (− 41.4%) HDL-C (+ 8.7%) TG (− 15%)	Change in PAV by IVUS	− 0.99% (95% CI − 1.19 to − 0.63) in the atorvastatin group
			Intensive therapy Rosuvastatin 40 mg/days 2.0 years	TC (− 28.1%) LDL-C (− 47.8%) HDL-C (+ 11.2%) TG (− 6.2%)		− 1.22% (95% CI − 1.52 to − 0.90) in the rosuvastatin group

4S Scandinavian Simvastatin Survival Study, CHD coronary heart disease, *mg/d* milligram per day, y year, *TC* total cholesterol, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, *TG* triglycerides, RR relative risk, CI confidence interval, WOSCOP West of Scotland Coronary Prevention, MI myocardial infarction, RRR relative risk reduction, CARE Cholesterol and Recurrent Events, *AFCAPS/TexCAPS* Air Force/Texas Coronary Atherosclerosis Prevention Study, *LIPID* Long-Term Intervention with Pravastatin in Ischaemic Disease, *PROSPER* PROspective Study of Pravastatin in the Elderly at Risk, *CVD* cardiovascular disease, HR hazard ratio, *ASCOT-LLA* Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm, *CARDS* Collaborative Atorvastatin Diabetes Study, PROVE-IT TIMI 22 Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction, *RHR* reduction in the hazard ratio, ASTEROID A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound – Derived Coronary Atheroma Burden, IVUS intravascular ultrasonography, PAV percentage atheroma volume, *JUPITER* Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin, *hsCRP* high-sensitivity C-reactive protein, SATURN The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin

showed non-significant differences in aortic stenosis compared to statin alone (Kastelein et al. 2005; Rossebø et al. 2008), recent trials revealed beneficial effects of ezetimibe/statin combination therapy in patients with ASCVD (Baigent et al. 2011; Cannon et al. 2015; Tsujita et al. 2015). A combination therapy of ezetimibe (10 mg/day) and simvastatin (40 mg/day) improved Kaplan–Meier event rates of the primary study end point by 2% compared to simvastatin monotherapy in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) (Cannon et al. 2015), and ezetimibe/atorvastatin combination resulted in greater coronary plaque regression than atorvastatin monotherapy in the Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound (PRECISE-IVUS) study (Tsujita et al. 2015). These studies support the use of ezetimibe as second line therapy for statin-intolerant patients with ASCVD.

PCSK9 inhibitor

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease highly expressed in the liver and binds to LDL-R to catalyze its degradation in lysosomes, leading to elevated LDL-C level in serum (Seidah et al. 2014). Abifadel et al. reported that a gain-of-function by missense mutation of the PCSK9 gene in a French family caused autosomal dominant hypercholesterolemia (ADH), which is characterized by increase in LDL-C level (Abifadel et al. 2003). In contrast, loss-of-function mutations due to two nonsense mutations (Y142X and C679X) in the PCSK9 gene decrease serum LDL-C level in African-Americans, and Cohen et al. found that nonsense mutations in PCSK9 reduced the incidence of coronary events (Cohen et al. 2005, 2006). Therefore, clinical development programs are focusing on developing therapeutic antagonists of PCSK9 (Table 3).

Two fully human monoclonal antibodies (AMG145 = evolocumab and REGN727 = alirocumab) were validated as inhibitors of PCSK9 in terms of efficacy and safety in patient trials (Robinson et al. 2015; Sabatine et al. 2015). Evolocumab plus standard therapy reduced LDL-C level by 61% and rate of CVD events from 2.18% after standard therapy to 0.95% in patients at high risk for CVD events (Sabatine et al. 2015). Combination therapy of alirocumab and statins at the maximum tolerated dose produced a 62% change from baseline in LDL-C level and reduced the rate of CVD events compared to single therapy in patients at high risk for CVD events (Robinson et al. 2015). The two antibodies have been verified for safety and efficacy for patients at high risk for CVD in several clinical trials (Navarese et al. 2015; Nicholls et al. 2016). Further, combination therapy with PCSK9 inhibitor was examined in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial of evolocumab and in the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes) trial of alirocumab, in which statins were associated with significantly reduced serum LDL-C level and a composite endpoint of cardiovascular death without major adverse effects in stable or unstable ASCVD patients, respectively (Sabatine et al. 2017; Schwartz et al. 2018).

In the ORION-1 clinical trial, inclisiran, a synthesized small interfering RNA targeting PCSK9 messenger RNA (mRNA), produced promising results in that both single-dose regimens (200, 300, or 500 mg of inclisiran) and two-dose regimens (100, 200, or 300 mg of inclisiran) maintained reductions of PCSK9 (single-dose regimen, from 47.9 to 59.3% and two-dose regimen, 53.2 to 69.1%) and LDL-C level (single-dose regimen, from 27.9 to 41.9% and two-dose regimen, 35.5 to 52.6%) at day 180 (Ray et al. 2017). In comparison with monoclonal antibodies, inclisiran has the potential advantage of decreasing the number of injections and amount of drug required for therapeutic effect.

Omega-3 polyunsaturated fatty acids

Omega-3 polyunsaturated fatty acids (PUFAs) have beneficial effects including lowering TG, enhancing endothelial function, vasodilation, decreasing platelet aggregation ability, and decreasing myocyte excitability (Mozaffarian and Wu 2012). Early clinical trials have shown beneficial effects of omega-3 PUFAs on mortality due to ASCVD (GISSI-Prevenzione Investigators 1999; Yokoyama et al. 2007; Tavazzi et al. 2008), but recent trials and meta-analyses failed to replicate the beneficial effects seen in early trials (Kromhout et al. 2010; Kwak et al. 2012). In a recent systematic review and meta-analysis of 20 studies of 63,630 subjects, Kotwal et al. concluded that omega-3 PUFAs had no overall effects on composite cardiovascular events such as myocardial infarction, stroke, or cardiovascular death [relative risk (RR) 0.96; 95% confidence interval (CI) 0.90–1.03; P = 0.24) or on total mortality (RR 0.95; 95% CI 0.86–1.04; P = 0.28) (Kotwal et al. 2012). However, omega-3 PUFAs exhibited protective effects against vascular death (RR 0.86; 95% CI 0.75–0.99; P = 0.03). In addition, the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDECE-IT) reported that a primary endpoint event occurred in 17.2% of patients treated with icosapent ethyl (total daily dose, 4 g) and purified and stable eicosapentaenoic acid (EPA) compared with 22.0% of the placebo group (Bhatt et al. 2019). The STatin Residual Risk Reduction With

Table 3 Summary of PCSK9 inhibition trials

Year	Clinical trial	Study size	Drug/dose/duration	Change in serum lipids from baseline	Primary endpoint	Results
2017	FOURIER (Sabatine et al. 2017)	27,564 patients with ASCVD and LDL-C (≥ 70 mg/dL)	Evolocumab (PCSK9 antibodies) 140 mg every 2 weeks or 420 mg monthely 2.2 years	TC (− 35.5%) LDL-C (− 59%) HDL-C (+ 8.4%) TG (− 16.2%) at 12 months	Combined CHD death/nonfatal acute MI	11.3% in the placebo group; 9.8% in the evolocumab group; HR 0.85, 95% CI 0.79–0.92
2017	SPIRE (Ridker et al. 2017b)	27,438 patients with CVD residual risk	Bococizumab (PCSK9 antibodies) 150 mg ever 2 weeks 10 months	TC (− 35.2%) LDL-C (− 56.0%) HDL-C (+7.6%) TG (− 13.6%) at 14 weeks	Combined death, MI, UAP, revascularization, stroke	Discontinued due to the development of high rates of antidrug antibodies
2017	ORION-1 (Ray et al. 2017)	501 patients with ASCVD or ASCVD-risk equivalents	Inclisiran (siRNA against PCSK9) A single dose (200, 300, 500 mg) or two doses (100, 200, 300 mg on day 1 and 90) Day 180	A single dose (300 mg) TC (− 23.7%) LDL-C (− 38.4%) HDL-C (+ 8.8%) TG (− 12.8%) at day 180 Two doses (300 mg) TC (− 33.2%) LDL-C (− 52.6%) HDL-C (+8.6%) TG (− 14.2%) at day 180	Change in LDL-C from baseline to day 180	A single dose (300 mg) PCSK9 (− 56.0%) at day 180 Two doses (300 mg) PCSK9 (− 69.1%) at day 180
2018	ODYSSEY OUTCMES (Schwartz et al. 2018)	18,924 patients with ACS	Alirocumab (PCSK9 antibodies) 75 mg every 2 weeks 2.8 years	LDL-C (− 61.0%) at 12 months	Combined CHD death/nonfatal acute MI	11.1% in the placebo group; 9.5% in the pravastatin group; HR 0.85, 95% CI 0.78–0.93%

FOURIER Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk, *ASCVD* Atherosclerotic Cardiovascular disease, LDL-C low-density lipoprotein cholesterol, *mg/dL* milligram per deciliter, *PCSK9* proprotein convertase subtilisin/kexin type 9, y year, *TC* total cholesterol, HDL-C high-density lipoprotein cholesterol, *TG* triglycerides, CHD coronary heart disease, MI myocardial infarction, HR hazard ratio, CI confidence interval, SPIRE Studies of PCSK9 Inhibition and the Reduction of Vascular Events, *CVD* cardiovascular disease, *UAP* unstable angina pectoris, *ORION-1* Trial to Evaluate the Effect of ALN-PCSSC Treatment on Low Density Lipoprotein Cholesterol, *siRNA* small interfering RNA, *ODYSSEY OUTCOMES* Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab

EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia study (STRENGTH), another large prospective randomized controlled outcomes trial planned for 2019, will determine whether Epanova (4 g/day) has beneficial effects against cardiovascular events in statin-treated high risk patients (Nicholls et al. 2018).

Other lipid-lowering agents

- *Bempedoic acid (ETC-1002)*

Adenosine triphosphate citrate lyase (ACL) is a cytosolic enzyme that is highly expressed in liver and white adipose tissue and is involved in fatty acid and cholesterol biosynthesis through catalyzing acetyl CoA synthesis

(Bilen and Ballantyne 2016). ETC-1002, which is a first-in-class, oral, once-daily, small molecule cholesterol synthesis inhibitor, has two major modes of action in inhibition of ACL and activation of AMP-activated protein kinase (AMPK) (Pinkosky et al. 2013). ETC-1002 lowered LDL-C level in patients with hypercholesterolemia by 30% when used as monotherapy, by 48% as part of a combination therapy with ezetimibe (10 mg), and by an additional 22% when used in combination with atorvastatin (10 mg) (Bilen and Ballantyne 2016; Thompson et al. 2016). In addition, ETC-1002 treatment increased the activity of AMPK, a metabolic sensor involved in gluconeogenesis, β-oxidation of fatty acids, mitochondrial density, and inflammatory signaling, resulting in clinical favorable effects on CVD risk factors including hyperglycemia and insulin resistance (Pinkosky et al. 2013; Bilen and Ballantyne 2016). Indeed, ETC-1002 treatment lowered LDL-C level (39%), fasting plasma glucose (− 8.5%), and hsCRP (41%) in patients with hypercholesterolemia and type 2 diabetes mellitus compared to placebo (Gutierrez et al. 2014). Pinkosky et al. demonstrated that ETC-1002 inhibits cholesterol biosynthesis in the liver but not in skeletal muscle because of the tissue distribution of very long-chain acyl-CoA synthetase-1 (ACSVL1), which modulates ETC-1002 (inactive form) to ETC-1002-CoA (active form) (Pinkosky et al. 2016). Thus, ETC-1002 is a potent drug for dramatically reducing the incidence of diabetes mellitus and myotoxicity associated with statin therapy.

Mipomersen

Mipomersen, a synthetic single-strand apoB antisense oligonucleotide (ASO), binds to mRNA coding for apoB-100 and accelerates the degradation of mRNA by the enzyme ribonuclease H (Bell et al. 2011). Mipomersen was developed to treat homozygous familial hypercholesterolemia (HoFH). In clinical trials, mipomersen reduced apoB level (25–34%), LDL-C level (28–36%), and Lp(a) (21–33%) in patients with HoFH, but 18% of patients receiving mipomersen stopped taking the drug due to adverse effects such as skin reactions at the injection site, liver damage, and flu-like symptoms (Raal et al. 2010; McGowan et al. 2012; Stein et al. 2012; Thomas et al. 2013).

Lomitapide

Lomitapide is a small molecule inhibitor of microsomal triglyceride transfer protein (MTP or MTTP), which transfers lipids to apoB in the endoplasmic reticulum to assemble very low-density lipoprotein (VLDL) and chylomicrons (Gregg and Wetterau 1994; Rader and Kastelein 2014). Lomitapide (40 mg/day) reduced level of LDL-C by 50% at 26 weeks and by 38% at week 78 in patients with HoFH, with adverse effects including gastrointestinal symptoms due to increased TG of enterocytes, hepatic fat accumulation, and elevation of transaminases (Cuchel et al. 2013).

Emerging targets

Angiopoietin-like 3 (ANGPTL3)

Loss-of-function mutations in the ANGPTL3 gene are associated with reductions of plasma TG, LDL-C, and HDL-C levels, inspiring the development of therapeutic agents targeting ANGPTL3 in ASCVD (Robciuc et al. 2013). ANGPTL3 acts as a dual inhibitor of lipoprotein lipase (LPL) and endothelial lipase (EL), resulting in elevation of plasma TG, LDL-C, and HDL-C levels (Fujimoto et al. 2006; Lee et al. 2009). In a clinical trial, ANGPTL3-LRx, an antisense inhibitor of ANGPTL3, resulted in reductions of TG (33.2% to 63.1%), LDL-C (1.3% to 32.9%), and total cholesterol (8.7% to 34.3%) in healthy adults (Graham et al. 2017). Dewey et al. verified that evinacumab, a human monoclonal antibody against ANGPTL3, decreased atheroma and necrotic core size compared to a control antibody in dyslipidemic mice, and that evinacumab reduced fasting TG level by 76% and LDL-C level by 23% in healthy human volunteers, highlighting its possible use as a new therapeutic agent against ASCVD (Dewey et al. 2017).

Lipoprotein(a)

Genetic studies and epidemiologic studies consistently suggest that Lp(a) is an independent risk factor for ASCVD (Danesh et al. 2000; Kamstrup et al. 2009). Lp(a) consists of one molecule of apo(a) linked to one molecule of apoB-100 of the LDL-like particle (Albers et al. 1996). Due to its structural similarity to plasminogen and tissue plasminogen activator (tPA), Lp(a) interferes with the fibrinolytic system and stimulates secretion of plasminogen activator inhibitor 1 (PAI-1), leading to atherothrombosis (Eaton et al. 1987). Lp(a) carries cholesterol and oxidized phospholipids, both of which contribute to progression of atherosclerosis through recruitment of inflammatory cells and proliferation of smooth muscle cells (Tsimikas et al. 2005; Banach 2016).

Although selective therapeutic agents that decrease Lp(a) without affecting other lipoproteins are not available, lipid-lowering drugs including niacin, mipomersen, lomitapide, PCSK9 inhibitors, cholesterol-ester-transfer protein (CETP) inhibitor, and atorvastatin reduce Lp(a) level and also affect other lipids and lipoproteins. In a phase 1/2a trial, IONIS-APO(a)-LRx, a ligand-conjugated antisense

oligonucleotide targeting apo(a) designed to be highly and selectively taken up by hepatocytes, resulted in mean reduction in Lp(a) by 66% in the 10 mg group, by 80% in the 20 mg group, and by 92% in the 40 mg group, without adverse effects (Viney et al. 2016). Therefore, IONIS-APO(a)-LRx may be a potent therapy to reduce Lp(a) concentration in patients with high Lp(a)-mediated ASCVD.

Anti-inflammation therapies

Despite the importance of cholesterol in ASCVD, more than 50% of ASCVD patients treated with lipid-lowering drugs still suffer from major ASCVD events and mortality even after achieving goal LDL-C level (Castelli 1996; Libby et al. 2000; Catapano et al. 2017; Jellinger et al. 2017). This convergence of clinical findings indicates the need to develop non-lipid-lowering drugs for treatment of ASCVD (Ridker and Luscher 2014; Ridker 2016). The underlying pathogenesis of atherosclerosis involves imbalanced lipid regulation and inflammatory response, and unleashed inflammation is closely related to initiation, progression, and thrombotic complications of atherosclerosis (Weber and Noels 2011). Indeed, modified LDL such as oxLDL and glycation of LDL evokes endothelial dysfunction and recruitment of immune cells into arterial walls, propagating atheroma (Libby et al. 2011; Park and Oh 2011). Maladaptive immune responses in advanced atherosclerosis deleteriously affect the resolution of inflammation, which leads to expansion of the necrotic core and plaque destabilization (Sakakura et al. 2013). Therefore, inflammation participates in all stages of atherosclerosis from initiation to progression to destabilization, suggesting that resolving inflammation by targeting pivotal pro- or anti-inflammatory molecules or cells may be useful for giving assistance to lipid-lowering therapies (Fig. 3). In this section, we review therapeutic agents and targets thought to resolve inflammation in ASCVD.

CANTOS trial: interleukin (IL)-1β neutralizing monoclonal antibody (canakinumab)

The interleukin-1 (IL-1) family, consisting of IL-1α and IL-1β isoforms, plays important roles in the pathogenesis of atherosclerosis such as increasing adhesion molecule expression on endothelial cells, triggering vascular smooth muscle cell proliferation, and up-regulating IL-6, which induces the elevation of several acute phase reactants including hsCRP, fibrinogen, and PAI-1 on hepatocytes (Bevilacqua et al. 1985; Libby et al. 1988; Ridker et al. 2012; Ridker and Luscher 2014; Ridker 2016; Libby 2017). Dysregulation of IL-1β activation by genetic mutations causes severe inflammation and fever (Mariathasan and Monack 2007), indicating that IL-1β is a key molecule in the inflammation pathway. Therefore, modulation of IL-1β may be effective in patients with ASCVD.

Canakinumab is a fully human monoclonal antibody neutralizing IL-1β that was approved for treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), which is a spectrum of auto-inflammatory syndromes including Muckle-Wells syndrome, familial cold auto-inflammatory syndrome, and neonatal-onset multisystem inflammatory

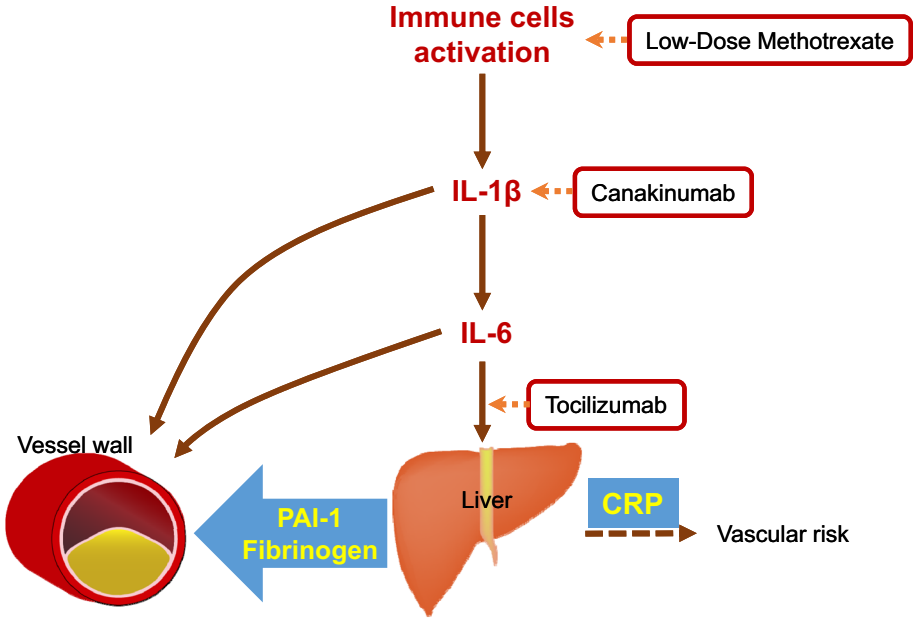

Fig. 3 Inflammatory pathways with potential uses as therapeutic targets for atherosclerotic cardiovascular disease (Modified from Ridker (2016)). *IL-1β* interleukin-1beta, *IL-6* interleukin-6, *PAI-1* plasminogen activator inhibitor type-1, *CRP* C-reactive protein, *hsCRP* high-sensitivity C-reactive protein

disease (Dinarello et al. 2012). In the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial, canakinumab (50, 150, 300 mg, administered subcutaneously every 3 months) was evaluated in patients with prior MI and high level of hsCRP (≥ 2 mg/L) (Ridker et al. 2017a, b; Aday and Ridker 2018). The primary end point was a composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. After 48 months, canakinumab treatment reduced hsCRP levels by 26% in the 50 mg group, by 37% in the 150 mg group, and by 41% in the 300 mg group compared to placebo, without affecting lipid levels. The incidence rate of the primary end point was 4.50 events per 100 person-years in the placebo group and 4.11, 3.86, and 3.90 events per 100 person-years in the 50, 150, and 300 mg groups, respectively. Therefore, anti-inflammatory therapy targeting IL-1β with canakinumab significantly reduced the rate of recurrent CVD events compared to placebo without affecting lipid levels.

Cardiovascular inflammation reduction trial (CIRT)

Low-dose methotrexate (10–30 mg/week) is broadly used to treat patients with cancer or autoimmune disease (Saag et al. 2008; Singh et al. 2012). When low-dose methotrexate treatment is used as an immune system suppressant in patients with rheumatologic disease, it reduces markers of inflammation, including CRP, IL-6, and tumor necrosis factor α (TNF α), without affecting lipid levels, blood pressure, or platelet function (Rho et al. 2009). In a meta-analysis, patients with rheumatologic disease receiving methotrexate treatment showed 21% lower risk of cardiovascular events compared to those receiving other anti-rheumatic therapies (Micha et al. 2011).

The CIRT is a randomized clinical trial to determine whether direct inhibition of inflammation by low-dose methotrexate (15-20 mg/week) had clinical relevance for anti-atherothrombosis in prior MI patients with type 2 diabetes or metabolic syndrome (Everett et al. 2013). The primary end point of the CIRT is a composite of nonfatal MI, nonfatal stroke, and cardiovascular death. The CIRT was stopped after 4786 patients of the planned 7000 patients had been enrolled, and the results are anticipated in 2018.

Interleukin-6 receptor (IL-6R) antagonist

IL-6 is a cytokine derived from immune cells, adipocytes, and smooth muscle cells (Tanaka et al. 2014). Although IL-6 acts as an anti-inflammatory myokine in muscle (Petersen and Pedersen 2005; Brandt and Pedersen 2010), it also stimulates inflammatory and auto-immune processes in several diseases including rheumatoid arthritis, diabetes, and atherosclerosis (Davies and Choy 2014; Tanaka et al. 2014). IL-6 is a major pro-inflammatory cytokine in the pathogenesis of atherosclerosis, stimulating production of CRP and fibrinogen from hepatocytes (Heinrich et al. 1990). Increased plasma IL-6 level is associated with mortality due to ASCVD independent of other risk factors, and genetic polymorphisms in the IL-6 signaling pathway at rs2228145 and rs7529229 are associated with lower levels of hsCRP and of vascular risk (IL6R Genetics Consortium Emerging Risk Factors Collaboration et al. 2012; Interleukin-6 Receptor Mendelian Randomisation Analysis et al. 2012).

Tocilizumab is a humanized monoclonal antibody against IL-6R that is used as an immunosuppressive drug for treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis (Fleischmann et al. 2013; Yokota et al. 2016). Despite promising observations, patients with rheumatoid arthritis who received tocilizumab exhibited significant increases of TC, LDL-C, and TG levels compared to a placebo group by week 12 (12.6% vs. 1.7%, 28.1% vs. 2.2%, 10.6% vs-1.9%, respectively), indicating major limitations in the development of IL-6 receptor antagonist treatments for ASCVD (Kawashiri et al. 2011; Strang et al. 2013).

Varespladib and darapladib

The phosholipase A2 superfamily, including secretory phospholipase A2 (sPLA2) and lipoprotein-associated phospholipase A2 (Lp-PLA2), hydrolyzes phospholipid molecules and produces potential atherogenic lipid fractions (Rosenson and Stafforini 2012). Thus, sPLA2 and Lp-PLA2 were considered potential risk factors for ASCVD in animal and observational human studies (Lp et al. 2010; Rosenson 2010; Rosenson and Hurt-Camejo 2012). However, clinical trials to evaluate the efficacy of varespladib (a non-specific sPLA2 inhibitor) and darapladib (a targeted Lp-PLA2 inhibitor) concluded that neither inhibitor had beneficial effects regarding risk of major coronary events (Mohler et al. 2008; Serruys et al. 2008; Rosenson et al. 2010). In addition, Holmes et al. reported that a genetic variant, the PLA2G2A rs 11573156 allele, was associated with reduction of sPLA2 level but not with major vascular events according to Mendelian randomization meta-analysis (Holmes et al. 2013), suggesting that sPLA2 is not a promising therapeutic target for preventing ASCVD.

Limitations and future directions

Currently, the efficacy and safety of canakinumab neutralizing IL-1β has been verified only for treatment of ASCVD. Low-dose methotrexate treatment for ASCVD is also promising in terms of efficacy and safety as a therapy

for ASCVD. However, many agonistic or antagonistic candidates in inflammation pathways have failed to develop into useful drugs for treating ASCVD due to the complexity of the specific inflammatory process. To surmount this hurdle, genome-wide association studies (GWAS) would be helpful to develop new therapeutic targets and drugs for ASCVD. Genetic variants in inflammation genes and coronary artery disease including C-X-C motif ligand 12 (CXCL12), SH2B adaptor protein 3 (SH2B3), AB0, Human Leukocyte Antigen (HLA), IL-5, Platelet endothelial cell adhesion molecule 1 (PECAM1), Protein C Receptor (PROCR), and antisense non-coding RNA in the INK4 locus (ANRIL) are potential targets for development of ASCVD therapeutic agents (Fava and Montagnana 2018). Based on the pathogenesis of atherosclerosis, studying targets regulating systemic and/or local lipid metabolism might be helpful to gain insights useful for development of drugs against ASCVD. A small number of adipokines, including adiponectin and retnla, exhibit anti-obesity and anti-inflammatory properties, leading to reduction of atherosclerosis in experimental studies (Okamoto et al. 2002, 2008; Lee et al. 2014). Recently, we proposed that oxidative stress activates macroautophagy/autophagy and contributes to atherogenesis via lipophagic flux, which maintains lowered intracellular cholesterol mass in macrophages (Jeong et al. 2018). This leads to the possibility of using oxidative stress as a novel therapeutic target to regulate macrophage cholesterol homeostasis against ASCVD.

Conclusion

The morbidity and mortality caused by ASCVD have been reduced by lowering LDL-C level through statin therapy, which is a great cornerstone for treatment and prevention of ASCVD. Combination therapies with statins and other lipid-lowering drugs including ezetimibe and PCSK9 inhibitors have yielded additive benefits for treatment of ASCVD. In addition, anti-inflammatory therapies, including canakinumab and low-dose methotrexate, hold promise due to their efficacy and safety for treatment of ASCVD. Although the rate of ASCVD events is significantly reduced by administration of current lipid-lowering drugs and anti-inflammatory agents, morbidity and mortality remain high in ASCVD patients. Constant efforts for development of new therapeutic targets based on GWAS and molecular lipid metabolism would pave the way to a new era of precision medicine for treatment of patients with ASCVD.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

References

Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derré A, Villéger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf JM, Luc G, Moulin P, Weissenbach J, Prat A, Krempf M, Junien C, Seidah NG, Boileau C (2003) Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 34(2):154–156. https://doi.org/10.1038/ng1161

Aday AW, Ridker PM (2018) Antiinflammatory therapy in clinical care: the CANTOS trial and beyond. Front Cardiovasc Med 5:62. https://doi.org/10.3389/fcvm.2018.00062

Albers JJ, Kennedy H, Marcovina SM (1996) Evidence that Lp[a] contains one molecule of apo[a] and one molecule of apoB: evaluation of amino acid analysis data. J Lipid Res 37(1):192–196

Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R, Investigators SHARP (2011) The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 377(9784):2181–2192. https://doi.org/10.1016/S0140-6736(11)60739-3

Banach M (2016) Lipoprotein (a)-we know so much yet still have much to learn. J Am Heart Assoc. https://doi.org/10.1161/JAHA.116.003597

Bell DA, Hooper AJ, Burnett JR (2011) Mipomersen, an antisense apolipoprotein B synthesis inhibitor. Expert Opin Investig Drugs 20(2):265–272. https://doi.org/10.1517/13543784.2011.547471

Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee (2018) Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation 137(12):e67–e492. https://doi.org/10.1161/CIR.0000000000000558

Bergheanu SC, Bodde MC, Jukema JW (2017) Pathophysiology and treatment of atherosclerosis: current view and future perspective

on lipoprotein modification treatment. Neth Heart J 25(4):231–242. https://doi.org/10.1007/s12471-017-0959-2

Bevilacqua MP, Pober JS, Wheeler ME, Cotran RS, Gimbrone MA Jr (1985) Interleukin-1 activation of vascular endothelium. Effects on procoagulant activity and leukocyte adhesion. Am J Pathol 121(3):394–403

Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM, REDUCE-IT Investigators (2019) Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. https://doi.org/10.1056/NEJMoa1812792

Bilen O, Ballantyne CM (2016) Bempedoic Acid (ETC-1002): an investigational inhibitor of ATP citrate lyase. Curr Atheroscler Rep 18(10):61. https://doi.org/10.1007/s11883-016-0611-4

Brandt C, Pedersen BK (2010) The role of exercise-induced myokines in muscle homeostasis and the defense against chronic diseases. J Biomed Biotechnol 2010:520258. https://doi.org/10.1155/2010/520258

Brown AG, Smale TC, King TJ, Hasenkamp R, Thompson RH (1976) Crystal and molecular structure of compactin, a new antifungal metabolite from Penicillium brevicompactum. J Chem Soc Perkin Trans 1(11):1165–1170

Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators (2004) Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 350(15):1495–1504. https://doi.org/10.1056/NEJMoa040583

Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM, Investigators IMPROVE-IT (2015) Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 372(25):2387–2397. https://doi.org/10.1056/NEJMoa1410489

Castelli WP (1996) Lipids, risk factors and ischaemic heart disease. Atherosclerosis 124(Suppl):S1–S9

Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Monique Verschuren WM, Vlachopoulos C, Wood DA, Luis Zamorano J, Contributor Additional, Cooney MT (2017) 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 37(39):2999–3058. https://doi.org/10.1093/eurheartj/ehw272

Chhatriwalla AK, Nicholls SJ, Nissen SE (2006) The ASTEROID trial: coronary plaque regression with high-dose statin therapy. Future Cardiol 2(6):651–654. https://doi.org/10.2217/14796678.2.6.651

Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R (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(9753):1670–1681. https://doi.org/10.1016/S0140-6736(10)61350-5

Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH (2005) Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet 37(2):161–165. https://doi.org/10.1038/ng1509

Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH (2006) Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 354(12):1264–1272. https://doi.org/10.1056/NEJMoa054013

Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH, CARDS investigators (2004) Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 364(9435):685–696. https://doi.org/10.1016/S0140-6736(04)16895-5

Cuchel M, Meagher EA, du Toit Theron H, Blom DJ, Marais AD, Hegele RA, Averna MR, Sirtori CR, Shah PK, Gaudet D, Stefanutti C, Vigna GB, Du Plessis AM, Propert KJ, Sasiela WJ, Bloedon LT, Rader DJ, Phase 3 HoFH Lomitapide Study investigators (2013) Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet 381(9860):40–46. https://doi.org/10.1016/S0140-6736(12)61731-0

Danesh J, Collins R, Peto R (2000) Lipoprotein(a) and coronary heart disease.Meta-analysis of prospective studies. Circulation 102(10):1082–1085

Davies R, Choy E (2014) Clinical experience of IL-6 blockade in rheumatic diseases - implications on IL-6 biology and disease pathogenesis. Semin Immunol 26(1):97–104. https://doi.org/10.1016/j.smim.2013.12.002

Dewey FE, Gusarova V, Dunbar RL, O'Dushlaine C, Schurmann C, Gottesman O, McCarthy S, Van Hout CV, Bruse S, Dansky HM, Leader JB, Murray MF, Ritchie MD, Kirchner HL, Habegger L, Lopez A, Penn J, Zhao A, Shao W, Stahl N, Murphy AJ, Hamon S, Bouzelmat A, Zhang R, Shumel B, Pordy R, Gipe D, Herman GA, Sheu WHH, Lee IT, Liang KW, Guo X, Rotter JI, Chen YI, Kraus WE, Shah SH, Damrauer S, Small A, Rader DJ, Wulff AB, Nordestgaard BG, Tybjærg-Hansen A, van den Hoek AM, Princen HMG, Ledbetter DH, Carey DJ, Overton JD, Reid JG, Sasiela WJ, Banerjee P, Shuldiner AR, Borecki IB, Teslovich TM, Yancopoulos GD, Mellis SJ, Gromada J, Baras A (2017) Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. N Engl J Med 377(3):211–221. https://doi.org/10.1056/NEJMoa1612790

Dinarello CA, Simon A, van der Meer JW (2012) Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. Nat Rev Drug Discov 11(8):633–652. https://doi.org/10.1038/nrd3800

Downs JR, Clearfield M, Weis S, Whitney E, Shapiro, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr (1998) Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 279(20):1615–1622

Eaton DL, Fless GM, Kohr WJ, McLean JW, Xu QT, Miller CG, Lawn RM, Scanu AM (1987) Partial amino acid sequence of apolipoprotein(a) shows that it is homologous to plasminogen. Proc Natl Acad Sci USA 84(10):3224–3228

Elam MB, Hunninghake DB, Davis KB, Garg R, Johnson C, Egan D, Kostis JB, Sheps DS, Brinton EA (2000) Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. Arterial disease multiple intervention trial. JAMA 284(10):1263–1270

Everett BM, Pradhan AD, Solomon DH, Paynter N, Macfadyen J, Zaharris E, Gupta M, Clearfield M, Libby P, Hasan AA, Glynn RJ, Ridker PM (2013) Rationale and design of the cardiovascular inflammation reduction trial: a test of the inflammatory hypothesis of atherothrombosis. Am Heart J 166(2):199–207. https://doi.org/10.1016/j.ahj.2013.03.018

Fava C, Montagnana M (2018) Atherosclerosis is an inflammatory disease which lacks a common anti-inflammatory therapy: how human genetics can help to this issue. A narrative review. Front Pharmacol 9:55. https://doi.org/10.3389/fphar.2018.00055

Finking G, Hanke H (1997) Nikolaj Nikolajewitsch Anitschkow (1885-1964) established the cholesterol-fed rabbit as a model for atherosclerosis research. Atherosclerosis 135(1):1–7

Fleischmann RM, Halland AM, Brzosko M, Burgos-Vargas R, Mela C, Vernon E, Kremer JM (2013) Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. J Rheumatol 40(2):113–126. https://doi.org/10.3899/jrheum.120447

Fujimoto K, Koishi R, Shimizugawa T, Ando Y (2006) Angptl3-null mice show low plasma lipid concentrations by enhanced lipoprotein lipase activity. Exp Anim 55(1):27–34

GISSI-Prevenzione Investigators (1999) Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 354(9177):447–455

Graham MJ, Lee RG, Brandt TA, Tai LJ, Fu W, Peralta R, Yu R, Hurh E, Paz E, McEvoy BW, Baker BF, Pham NC, Digenio A, Hughes SG, Geary RS, Witztum JL, Crooke RM, Tsimikas S (2017) Cardiovascular and Metabolic Effects of ANGPTL3 Antisense Oligonucleotides. N Engl J Med 377(3):222–232. https://doi.org/10.1056/NEJMoa1701329

Gregg RE, Wetterau JR (1994) The molecular basis of abetalipoproteinemia. Curr Opin Lipidol 5(2):81–86

Gutierrez MJ, Rosenberg NL, Macdougall DE, Hanselman JC, Margulies JR, Strange P, Milad MA, McBride SJ, Newton RS (2014) Efficacy and safety of ETC-1002, a novel investigational low-density lipoprotein-cholesterol-lowering therapy for the treatment of patients with hypercholesterolemia and type 2 diabetes mellitus. Arterioscler Thromb Vasc Biol 34(3):676–683. https://doi.org/10.1161/ATVBAHA.113.302677

Heinrich PC, Castell JV, Andus T (1990) Interleukin-6 and the acute phase response. Biochem J 265(3):621–636

Holmes MV, Simon T, Exeter HJ, Folkersen L, Asselbergs FW, Guardiola M, Cooper JA, Palmen J, Hubacek JA, Carruthers KF, Horne BD, Brunisholz KD, Mega JL, van Iperen EPA, Li M, Leusink M, Trompet S, Verschuren JJW, Hovingh GK, Dehghan A, Nelson CP, Kotti S, Danchin N, Scholz M, Haase CL, Rothenbacher D, Swerdlow DI, Kuchenbaecker KB, Staines-Urias E, Goel A, van 't Hooft F, Gertow K, de Faire U, Panayiotou AG, Tremoli E, Baldassarre D, Veglia F, Holdt LM, Beutner F, Gansevoort RT, Navis GJ, Mateo Leach I, Breitling LP, Brenner H, Thiery J, Dallmeier D, Franco-Cereceda A, Boer JMA, Stephens JW, Hofker MH, Tedgui A, Hofman A, Uitterlinden AG, Adamkova V, Pitha J, Onland-Moret NC, Cramer MJ, Nathoe HM, Spiering W, Klungel OH, Kumari M, Whincup PH, Morrow DA, Braund PS, Hall AS, Olsson AG, Doevendans PA, Trip MD, Tobin MD, Hamsten A, Watkins H, Koenig W, Nicolaides AN, Teupser D, Day INM, Carlquist JF, Gaunt TR, Ford I, Sattar N, Tsimikas S, Schwartz GG, Lawlor DA, Morris RW, Sandhu MS, Poledne R, Maitland-van der Zee AH, Khaw KT, Keating BJ, van der Harst P, Price JF, Mehta SR, Yusuf S, Witteman JCM, Franco OH, Jukema JW, de Knijff P, Tybjaerg-Hansen A, Rader DJ, Farrall M, Samani NJ, Kivimaki M, Fox KAA, Humphries SE, Anderson JL, Boekholdt SM, Palmer TM, Eriksson P, Paré G, Hingorani AD, Sabatine MS, Mallat Z, Casas JP, Talmud PJ (2013) Secretory phospholipase A(2)-IIA and cardiovascular disease: a mendelian randomization study. J Am Coll Cardiol 62(21):1966–1976. https://doi.org/10.1016/j.jacc.2013.06.044

IL6R Genetics Consortium Emerging Risk Factors Collaboration, Sarwar N, Butterworth AS, Freitag DF, Gregson J, Willeit P, Gorman DN, Gao P, Saleheen D, Rendon A, Nelson CP, Braund PS, Hall AS, Chasman DI, Tybjærg-Hansen A, Chambers JC, Benjamin EJ, Franks PW, Clarke R, Wilde AA, Trip MD, Steri M, Witteman JC, Qi L, van der Schoot CE, de Faire U, Erdmann J, Stringham HM, Koenig W, Rader DJ, Melzer D, Reich D, Psaty BM, Kleber ME, Panagiotakos DB, Willeit J, Wennberg P, Woodward M, Adamovic S, Rimm EB, Meade TW, Gillum RF, Shaffer JA, Hofman A, Onat A, Sundström J, Wassertheil-Smoller S, Mellström D, Gallacher J, Cushman M, Tracy RP, Kauhanen J, Karlsson M, Salonen JT, Wilhelmsen L, Amouyel P, Cantin B, Best LG, Ben-Shlomo Y, Manson JE, Davey-Smith G, de Bakker PI, O'Donnell CJ, Wilson JF, Wilson AG, Assimes TL, Jansson JO, Ohlsson C, Tivesten Å, Ljunggren Ö, Reilly MP, Hamsten A, Ingelsson E, Cambien F, Hung J, Thomas GN, Boehnke M, Schunkert H, Asselbergs FW, Kastelein JJ, Gudnason V, Salomaa V, Harris TB, Kooner JS, Allin KH, Nordestgaard BG, Hopewell JC, Goodall AH, Ridker PM, Hólm H, Watkins H, Ouwehand WH, Samani NJ, Kaptoge S, Di Angelantonio E, Harari O, Danesh J (2012) Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. Lancet 379(9822):1205–1213. https://doi.org/10.1016/S0140-6736(11)61931-4

Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium, Swerdlow DI, Holmes MV, Kuchenbaecker KB, Engmann JE, Shah T, Sofat R, Guo Y, Chung C, Peasey A, Pfister R, Mooijaart SP, Ireland HA, Leusink M, Langenberg C, Li KW, Palmen J, Howard P, Cooper JA, Drenos F, Hardy J, Nalls MA, Li YR, Lowe G, Stewart M, Bielinski SJ, Peto J, Timpson NJ, Gallacher J, Dunlop M, Houlston R, Tomlinson I, Tzoulaki I, Luan J, Boer JM, Forouhi NG, Onland-Moret NC, van der Schouw YT, Schnabel RB, Hubacek JA, Kubinova R, Baceviciene M, Tamosiunas A, Pajak A, Topor-Madry R, Malyutina S, Baldassarre D, Sennblad B, Tremoli E, de Faire U, Ferrucci L, Bandenelli S, Tanaka T, Meschia JF, Singleton A, Navis G, Mateo Leach I, Bakker SJ, Gansevoort RT, Ford I, Epstein SE, Burnett MS, Devaney JM, Jukema JW, Westendorp RG, Jan de Borst G, van der Graaf Y, de Jong PA, Mailand-van der Zee AH, Klungel OH, de Boer A, Doevendans PA, Stephens JW, Eaton CB, Robinson JG, Manson JE, Fowkes FG, Frayling TM, Price JF, Whincup PH, Morris RW, Lawlor DA, Smith GD, Ben-Shlomo Y, Redline S, Lange LA, Kumari M, Wareham NJ, Verschuren WM, Benjamin EJ, Whittaker JC, Hamsten A, Dudbridge F, Delaney JA, Wong A, Kuh D, Hardy R, Castillo BA, Connolly JJ, van der Harst P, Brunner EJ, Marmot MG, Wassel CL, Humphries SE, Talmud PJ, Kivimaki M, Asselbergs FW, Voevoda M, Bobak M, Pikhart H, Wilson JG, Hakonarson H, Reiner AP, Keating BJ, Sattar N, Hingorani AD, Casas JP (2012) The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. Lancet 379(9822):1214–1224. https://doi.org/10.1016/S0140-6736(12)60110-X

Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DSH, Mechanick JI, Pessah-Pollack R, Wyne K, Smith D, Brinton EA, Fazio S, Davidson M, Zangeneh F, Bush MA. (2017) American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease–Executive Summary. Endocr Pract 23(4):479-497 https://doi.org/10.4158/ep171764.gl. Complete Appendix to Guidelines http://journals.aace.com

Jeong SJ, Kim S, Park JG, Jung IH, Lee MN, Jeon S, Kweon HY, Yu DY, Lee SH, Jang Y, Kang SW, Han KH, Miller YI, Park YM, Cheong C, Choi JH, Oh GT (2018) Prdx1 (peroxiredoxin 1) deficiency reduces cholesterol efflux via impaired macrophage lipophagic flux. Autophagy 14(1):120–133. https://doi.org/10.1080/15548627.2017.1327942

Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG (2009) Genetically elevated lipoprotein(a) and increased risk of

myocardial infarction. JAMA 301(22):2331–2339. https://doi.org/10.1001/jama.2009.801

Kastelein JJ, Sager PT, de Groot E, Veltri E (2005) Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia. Design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial. Am Heart J 149(2):234–239. https://doi.org/10.1016/j.ahj.2004.06.024

Kawashiri SY, Kawakami A, Yamasaki S, Imazato T, Iwamoto N, Fujikawa K, Aramaki T, Tamai M, Nakamura H, Ida H, Origuchi T, Ueki Y, Eguchi K (2011) Effects of the anti-interleukin-6 receptor antibody, tocilizumab, on serum lipid levels in patients with rheumatoid arthritis. Rheumatol Int 31(4):451–456. https://doi.org/10.1007/s00296-009-1303-y

Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B (2012) Omega 3 Fatty acids and cardiovascular outcomes: systematic review and meta-analysis. Circ Cardiovasc Qual Outcome 5(6):808–818. https://doi.org/10.1161/CIRCOUTCOMES.112.966168

Kromhout D, Giltay EJ, Geleijnse JM, Alpha Omega Trial G (2010) n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med 363(21):2015–2026. https://doi.org/10.1056/NEJMoa1003603

Kronenberg F, Utermann G (2013) Lipoprotein(a): resurrected by genetics. J Intern Med 273(1):6–30. https://doi.org/10.1111/j.1365-2796.2012.02592.x

Kwak SM, Myung SK, Lee YJ, Seo HG, Korean Meta-analysis Study G (2012) Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. Arch Intern Med 172(9):686–694. https://doi.org/10.1001/archinternmed.2012.262

Kwon GP, Schroeder JL, Amar MJ, Remaley AT, Balaban RS (2008) Contribution of macromolecular structure to the retention of low-density lipoprotein at arterial branch points. Circulation 117(22):2919–2927. https://doi.org/10.1161/CIRCULATIONAHA.107.754614

Lee EC, Desai U, Gololobov G, Hong S, Feng X, Yu XC, Gay J, Wilganowski N, Gao C, Du LL, Chen J, Hu Y, Zhao S, Kirkpatrick L, Schneider M, Zambrowicz BP, Landes G, Powell DR, Sonnenburg WK (2009) Identification of a new functional domain in angiopoietin-like 3 (ANGPTL3) and angiopoietin-like 4 (ANGPTL4) involved in binding and inhibition of lipoprotein lipase (LPL). J Biol Chem 284(20):13735–13745. https://doi.org/10.1074/jbc.M807899200

Lee MR, Lim CJ, Lee YH, Park JG, Sonn SK, Lee MN, Jung IH, Jeong SJ, Jeon S, Lee M, Oh KS, Yang Y, Kim JB, Choi HS, Jeong W, Jeong TS, Yoon WK, Kim HC, Choi JH, Oh GT (2014) The adipokine Retnla modulates cholesterol homeostasis in hyperlipidemic mice. Nat Commun 5:4410. https://doi.org/10.1038/ncomms5410

Libby P (2017) Interleukin-1 beta as a target for atherosclerosis therapy: biological basis of CANTOS and beyond. J Am Coll Cardiol 70(18):2278–2289. https://doi.org/10.1016/j.jacc.2017.09.028

Libby P, Warner SJ, Friedman GB (1988) Interleukin 1: a mitogen for human vascular smooth muscle cells that induces the release of growth-inhibitory prostanoids. J Clin Investig 81(2):487–498. https://doi.org/10.1172/JCI113346

Libby P, Aikawa M, Schonbeck U (2000) Cholesterol and atherosclerosis. Biochem Biophys Acta 1529(1–3):299–309

Libby P, Ridker PM, Hansson GK (2011) Progress and challenges in translating the biology of atherosclerosis. Nature 473(7347):317–325. https://doi.org/10.1038/nature10146

Long-Term Intervention with Pravastatin in Ischaemic Disease Study G (1998) Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 339(19):1349–1357. https://doi.org/10.1056/NEJM199811053391902

Lp-PLA(2) Studies Collaboration, Thompson A, Gao P, Orfei L, Watson S, Di Angelantonio E, Kaptoge S, Ballantyne C, Cannon CP, Criqui M, Cushman M, Hofman A, Packard C, Thompson SG, Collins R, Danesh J (2010) Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet 375(9725):1536–1544. https://doi.org/10.1016/S0140-6736(10)60319-4

Mariathasan S, Monack DM (2007) Inflammasome adaptors and sensors: intracellular regulators of infection and inflammation. Nat Rev Immunol 7(1):31–40. https://doi.org/10.1038/nri1997

McGowan MP, Tardif JC, Ceska R, Burgess LJ, Soran H, Gouni-Berthold I, Wagener G, Chasan-Taber S (2012) Randomized, placebo-controlled trial of mipomersen in patients with severe hypercholesterolemia receiving maximally tolerated lipid-lowering therapy. PLoS ONE 7(11):e49006. https://doi.org/10.1371/journal.pone.0049006

Micha R, Imamura F, Wyler von Ballmoos M, Solomon DH, Hernán MA, Ridker PM, Mozaffarian D (2011) Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. Am J Cardiol 108(9):1362–1370. https://doi.org/10.1016/j.amjcard.2011.06.054

Mills EJ, O'Regan C, Eyawo O, Wu P, Mills F, Berwanger O, Briel M (2011) Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of > 40 000 patients. Eur Heart J 32(11):1409–1415. https://doi.org/10.1093/eurheartj/ehr035

Mohler ER 3rd, Ballantyne CM, Davidson MH, Hanefeld M, Ruilope LM, Johnson JL, Zalewski A, Investigators Darapladib (2008) The effect of darapladib on plasma lipoprotein-associated phospholipase A2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart disease risk equivalent: the results of a multicenter, randomized, double-blind, placebo-controlled study. J Am Coll Cardiol 51(17):1632–1641. https://doi.org/10.1016/j.jacc.2007.11.079

Moore KJ, Tabas I (2011) Macrophages in the pathogenesis of atherosclerosis. Cell 145(3):341–355. https://doi.org/10.1016/j.cell.2011.04.005

Mozaffarian D, Wu JH (2012) (n-3) fatty acids and cardiovascular health: are effects of EPA and DHA shared or complementary? J Nutr 142(3):614S–625S. https://doi.org/10.3945/jn.111.149633

Navarese EP, Kolodziejczak M, Schulze V, Gurbel PA, Tantry U, Lin Y, Brockmeyer M, Kandzari DE, Kubica JM, D'Agostino RB Sr, Kubica J, Volpe M, Agewall S, Kereiakes DJ, Kelm M (2015) Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. Ann Intern Med 163(1):40–51. https://doi.org/10.7326/M14-2957

Nelson RH (2013) Hyperlipidemia as a risk factor for cardiovascular disease. Prim Care 40(1):195–211. https://doi.org/10.1016/j.pop.2012.11.003

Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, Raichlen JS, Uno K, Borgman M, Wolski K, Nissen SE (2011) Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med 365(22):2078–2087. https://doi.org/10.1056/NEJMoa1110874

Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, Koenig W, Somaratne R, Kassahun H, Yang J, Wasserman SM, Scott R, Ungi I, Podolec J, Ophuis AO, Cornel JH, Borgman M, Brennan DM, Nissen SE (2016) Effect of evolocumab on

progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. JAMA 316(22):2373–2384. https://doi.org/10.1001/jama.2016.16951

Nicholls SJ, Lincoff AM, Bash D, Ballantyne CM, Barter PJ, Davidson MH, Kastelein JJP, Koenig W, McGuire DK, Mozaffarian D, Pedersen TR, Ridker PM, Ray K, Karlson BW, Lundström T, Wolski K, Nissen SE (2018) 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 41(10):1281–1288. https://doi.org/10.1002/clc.23055

Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, Kumada M, Ohashi K, Sakai N, Shimomura I, Kobayashi H, Terasaka N, Inaba T, Funahashi T, Matsuzawa Y (2002) Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. Circulation 106(22):2767–2770

Okamoto Y, Folco EJ, Minami M, Wara AK, Feinberg MW, Sukhova GK, Colvin RA, Kihara S, Funahashi T, Luster AD, Libby P (2008) Adiponectin inhibits the production of CXC receptor 3 chemokine ligands in macrophages and reduces T-lymphocyte recruitment in atherogenesis. Circ Res 102(2):218–225. https://doi.org/10.1161/CIRCRESAHA.107.164988

Pandor A, Ara RM, Tumur I, Wilkinson AJ, Paisley S, Duenas A, Durrington PN, Chilcott J (2009) Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. J Intern Med 265(5):568–580. https://doi.org/10.1111/j.1365-2796.2008.02062.x

Park JG, Oh GT (2011) The role of peroxidases in the pathogenesis of atherosclerosis. BMB Rep 44(8):497–505

Pedersen TR, Kjekshus J, Berg K, Haghfelt T, Faergeman O, Faergeman G, Pyörälä K, Miettinen T, Wilhelmsen L, Olsson AG, Wedel H, Scandinavian Simvastatin Survival Study Group (1994) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 344(8934):1383–1389

Petersen AM, Pedersen BK (2005) The anti-inflammatory effect of exercise. J Appl Physiol 98(4):1154–1162. https://doi.org/10.1152/japplphysiol.00164.2004

Phan BA, Dayspring TD, Toth PP (2012) Ezetimibe therapy: mechanism of action and clinical update. Vasc Health Risk Manage 8:415–427. https://doi.org/10.2147/VHRM.S33664

Pinkosky SL, Filippov S, Srivastava RA, Hanselman JC, Bradshaw CD, Hurley TR, Cramer CT, Spahr MA, Brant AF, Houghton JL, Baker C, Naples M, Adeli K, Newton RS (2013) AMP-activated protein kinase and ATP-citrate lyase are two distinct molecular targets for ETC-1002, a novel small molecule regulator of lipid and carbohydrate metabolism. J Lipid Res 54(1):134–151. https://doi.org/10.1194/jlr.M030528

Pinkosky SL, Newton RS, Day EA, Ford RJ, Lhotak S, Austin RC, Birch CM, Smith BK, Filippov S, Groot PH, Steinberg GR, Lalwani ND (2016) Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. Nat Commun 7:13457. https://doi.org/10.1038/ncomms13457

Raal FJ, Santos RD, Blom DJ, Marais AD, Charng MJ, Cromwell WC, Lachmann RH, Gaudet D, Tan JL, Chasan-Taber S, Tribble DL, Flaim JD, Crooke ST (2010) Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet 375(9719):998–1006. https://doi.org/10.1016/S0140-6736(10)60284-X

Rader DJ, Kastelein JJ (2014) Lomitapide and mipomersen: two first-in-class drugs for reducing low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia. Circulation 129(9):1022–1032. https://doi.org/10.1161/CIRCULATIONAHA.113.001292

Ray KK, Landmesser U, Leiter LA, Kallend D, Dufour R, Karakas M, Hall T, Troquay RP, Turner T, Visseren FL, Wijngaard P, Wright RS, Kastelein JJ (2017) Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med 376(15):1430–1440. https://doi.org/10.1056/NEJMoa1615758

Rho YH, Oeser A, Chung CP, Milne GL, Stein CM (2009) Drugs used in the treatment of rheumatoid arthritis: relationship between current use and cardiovascular risk factors. Arch Drug Inf 2(2):34–40. https://doi.org/10.1111/j.1753-5174.2009.00019.x

Ridker PM (2016) From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. Circ Res 118(1):145–156. https://doi.org/10.1161/CIRCRESAHA.115.306656

Ridker PM, Luscher TF (2014) Anti-inflammatory therapies for cardiovascular disease. Eur Heart J 35(27):1782–1791. https://doi.org/10.1093/eurheartj/ehu203

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ, JUPITER Study Group (2008) Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 359(21):2195–2207. https://doi.org/10.1056/NEJMoa0807646

Ridker PM, Howard CP, Walter V, Everett B, Libby P, Hensen J, Thuren T, CANTOS Pilot Investigative Group (2012) Effects of interleukin-1beta inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. Circulation 126(23):2739–2748. https://doi.org/10.1161/CIRCULATIONAHA.112.122556

Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, CANTOS Trial Group (2017a) Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 377(12):1119–1131. https://doi.org/10.1056/NEJMoa1707914

Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, Flather M, Glynn RJ, Gregoire J, Jukema JW, Karpov Y, Kastelein JJP, Koenig W, Lorenzatti A, Manga P, Masiukiewicz U, Miller M, Mosterd A, Murin J, Nicolau JC, Nissen S, Ponikowski P, Santos RD, Schwartz PF, Soran H, White H, Wright RS, Vrablik M, Yunis C, Shear CL, Tardif JC, SPIRE Cardiovascular Outcome Investigators (2017b) Cardiovascular efficacy and safety of bococizumab in high-risk patients. N Engl J Med 376(16):1527–1539. https://doi.org/10.1056/NEJMoa1701488

Robciuc MR, Maranghi M, Lahikainen A, Rader D, Bensadoun A, Öörni K, Metso J, Minicocci I, Ciociola E, Ceci F, Montali A, Arca M, Ehnholm C, Jauhiainen M (2013) Angptl3 deficiency is associated with increased insulin sensitivity, lipoprotein lipase activity, and decreased serum free fatty acids. Arterioscler Thromb Vasc Biol 33(7):1706–1713. https://doi.org/10.1161/ATVBAHA.113.301397

Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ, ODYSSEY LONG TERM Investigators (2015) Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 372(16):1489–1499. https://doi.org/10.1056/NEJMoa1501031

Rosenson RS (2010) Phospholipase A2 inhibition and atherosclerotic vascular disease: prospects for targeting secretory and lipoprotein-associated phospholipase A2 enzymes. Curr Opin Lipidol 21(6):473–480. https://doi.org/10.1097/MOL.0b013e32833eb581

Rosenson RS, Hurt-Camejo E (2012) Phospholipase A2 enzymes and the risk of atherosclerosis. Eur Heart J 33(23):2899–2909. https://doi.org/10.1093/eurheartj/ehs148

Rosenson RS, Stafforini DM (2012) Modulation of oxidative stress, inflammation, and atherosclerosis by lipoprotein-associated phospholipase A2. J Lipid Res 53(9):1767–1782. https://doi.org/10.1194/jlr.R024190

Rosenson RS, Hislop C, Elliott M, Stasiv Y, Goulder M, Waters D (2010) Effects of varespladib methyl on biomarkers and major cardiovascular events in acute coronary syndrome patients. J Am Coll Cardiol 56(14):1079–1088. https://doi.org/10.1016/j.jacc.2010.06.015

Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, Gerdts E, Gohlke-Bärwolf C, Holme I, Kesäniemi YA, Malbecq W, Nienaber CA, Ray S, Skjaerpe T, Wachtell K, Willenheimer R, SEAS Investigators (2008) Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 359(13):1343–1356. https://doi.org/10.1056/NEJMoa0804602

Rubin EM, Krauss RM, Spangler EA, Verstuyft JG, Clift SM (1991) Inhibition of early atherogenesis in transgenic mice by human apolipoprotein AI. Nature 353(6341):265–267. https://doi.org/10.1038/353265a0

Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, Paulus HE, Mudano A, Pisu M, Elkins-Melton M, Outman R, Allison JJ, Suarez Almazor M, Bridges SL Jr, Chatham WW, Hochberg M, MacLean C, Mikuls T, Moreland LW, O'Dell J, Turkiewicz AM, Furst DE, American College of Rheumatology (2008) American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthr Rheum 59(6):762–784. https://doi.org/10.1002/art.23721

Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J, Wasserman SM, Scott R, Koren MJ, Stein EA, Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators (2015) Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med 372(16):1500–1509. https://doi.org/10.1056/NEJMoa1500858

Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, FOURIER Steering Committee and Investigators (2017) Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 376(18):1713–1722. https://doi.org/10.1056/NEJMoa1615664

Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E (1996) The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 335(14):1001–1009. https://doi.org/10.1056/NEJM199610033351401

Sakakura K, Nakano M, Otsuka F, Ladich E, Kolodgie FD, Virmani R (2013) Pathophysiology of atherosclerosis plaque progression. Heart Lung Circ 22(6):399–411. https://doi.org/10.1016/j.hlc.2013.03.001

Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM, ODYSSEY OUTCOMES Committees and Investigators (2018) Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. https://doi.org/10.1056/NEJMoa1801174

Seidah NG, Awan Z, Chretien M, Mbikay M (2014) PCSK9: a key modulator of cardiovascular health. Circ Res 114(6):1022–1036. https://doi.org/10.1161/CIRCRESAHA.114.301621

Serruys PW, García-García HM, Buszman P, Erne P, Verheye S, Aschermann M, Duckers H, Bleie O, Dudek D, Bøtker HE, von Birgelen C, D'Amico D, Hutchinson T, Zambanini A, Mastik F, van Es GA, van der Steen AF, Vince DG, Ganz P, Hamm CW, Wijns W, Zalewski A, Integrated Biomarker and Imaging Study-2 Investigators (2008) Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. Circulation 118(11):1172–1182. https://doi.org/10.1161/CIRCULATIONAHA.108.771899

Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J, ASCOT investigators (2003) Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 361(9364):1149–1158. https://doi.org/10.1016/S0140-6736(03)12948-0

Shapiro MD, Fazio S (2016) From lipids to inflammation: new approaches to reducing atherosclerotic risk. Circ Res 118(4):732–749. https://doi.org/10.1161/CIRCRESAHA.115.306471

Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ (1995) Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 333(20):1301–1307. https://doi.org/10.1056/NEJM199511163332001

Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG, PROSPER study group, PROspective Study of Pravastatin in the Elderly at Risk (2002) Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 360(9346):1623–1630

Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, Moreland LW, O'Dell J, Winthrop KL, Beukelman T, Bridges SL Jr, Chatham WW, Paulus HE, Suarez-Almazor M, Bombardier C, Dougados M, Khanna D, King CM, Leong AL, Matteson EL, Schousboe JT, Moynihan E, Kolba KS, Jain A, Volkmann ER, Agrawal H, Bae S, Mudano AS, Patkar NM, Saag KG (2012) 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 64(5):625–639. https://doi.org/10.1002/acr.21641

Stein EA, Dufour R, Gagne C, Gaudet D, East C, Donovan JM, Chin W, Tribble DL, McGowan M (2012) Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo-controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. Circulation 126(19):2283–2292. https://doi.org/10.1161/CIRCULATIONAHA.112.104125

Strang AC, Bisoendial RJ, Kootte RS, Schulte DM, Dallinga-Thie GM, Levels JH, Kok M, Vos K, Tas SW, Tietge UJ, Müller N, Laudes M, Gerlag DM, Stroes ES, Tak PP (2013) Pro-atherogenic lipid changes and decreased hepatic LDL receptor

expression by tocilizumab in rheumatoid arthritis. Atherosclerosis 229(1):174–181. https://doi.org/10.1016/j.atherosclerosis.2013.04.031

Tanaka T, Narazaki M, Kishimoto T (2014) IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol 6(10):a016295. https://doi.org/10.1101/cshperspect.a016295

Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G, Gissi-HF Investigators (2008) Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 372(9645):1223–1230. https://doi.org/10.1016/S0140-6736(08)61239-8

Thomas GS, Cromwell WC, Ali S, Chin W, Flaim JD, Davidson M (2013) Mipomersen, an apolipoprotein B synthesis inhibitor, reduces atherogenic lipoproteins in patients with severe hypercholesterolemia at high cardiovascular risk: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol 62(23):2178–2184. https://doi.org/10.1016/j.jacc.2013.07.081

Thompson PD, MacDougall DE, Newton RS, Margulies JR, Hanselman JC, Orloff DG, McKenney JM, Ballantyne CM (2016) Treatment with ETC-1002 alone and in combination with ezetimibe lowers LDL cholesterol in hypercholesterolemic patients with or without statin intolerance. J Clin Lipidol 10(3):556–567. https://doi.org/10.1016/j.jacl.2015.12.025

Tsimikas S, Brilakis ES, Miller ER, McConnell JP, Lennon RJ, Kornman KS, Witztum JL, Berger PB (2005) Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. N Engl J Med 353(1):46–57. https://doi.org/10.1056/NEJMoa043175

Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, Komura N, Sakamoto K, Oka H, Nakao K, Nakamura S, Ishihara M, Matsui K, Sakaino N, Nakamura N, Yamamoto N, Koide S, Matsumura T, Fujimoto K, Tsunoda R, Morikami Y, Matsuyama K, Oshima S, Kaikita K, Hokimoto S, Ogawa H, PRECISE–IVUS Investigators (2015) Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: the multicenter randomized controlled PRECISE-IVUS trial. J Am Coll Cardiol 66(5):495–507. https://doi.org/10.1016/j.jacc.2015.05.065

Viney NJ, van Capelleveen JC, Geary RS, Xia S, Tami JA, Yu RZ, Marcovina SM, Hughes SG, Graham MJ, Crooke RM, Crooke ST, Witztum JL, Stroes ES, Tsimikas S (2016) Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet 388(10057):2239–2253. https://doi.org/10.1016/S0140-6736(16)31009-1

Weber C, Noels H (2011) Atherosclerosis: current pathogenesis and therapeutic options. Nat Med 17(11):1410–1422. https://doi.org/10.1038/nm.2538

Ylä-Herttuala S, Bentzon JF, Daemen M, Falk E, Garcia-Garcia HM, Herrmann J, Hoefer I, Jukema JW, Krams R, Kwak BR, Marx N, Naruszewicz M, Newby A, Pasterkamp G, Serruys PW, Waltenberger J, Weber C, Tokgözoglu L (2011) Stabilisation of atherosclerotic plaques. Position paper of the European Society of Cardiology (ESC) Working Group on atherosclerosis and vascular biology. Thromb Haemost 106(1):1–19. https://doi.org/10.1160/TH10-12-0784

Yokota S, Itoh Y, Morio T, Origasa H, Sumitomo N, Tomobe M, Tanaka K, Minota S (2016) Tocilizumab in systemic juvenile idiopathic arthritis in a real-world clinical setting: results from 1 year of postmarketing surveillance follow-up of 417 patients in Japan. Ann Rheum Dis 75(9):1654–1660. https://doi.org/10.1136/annrheumdis-2015-207818

Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Japan EPA lipid intervention study (JELIS) Investigators (2007) Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 369(9567):1090–1098. https://doi.org/10.1016/S0140-6736(07)60527-3