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Prevention (K Aragam, Section Editor)

Optimal Non-invasive Strategies to Reduce Recurrent Atherosclerotic Cardiovascular Disease Risk

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Abstract

Purpose of review Cardiovascular disease (CVD) remains the leading cause of death worldwide, with coronary artery disease (CAD) responsible for the vast majority of these deaths. Incidence is increasing in developing countries, and prevalence is increasing globally as populations age. Once CAD is manifest, recurrent event risk remains high.
Recent findings Multiple therapeutic avenues have had significant recent developments, including diet, low-density lipoprotein cholesterol management, triglycerides, hypoglycemic agents, antiplatelet agents, and oral anticoagulants.
Summary Combined approaches involving specific, tailored lifestyle, and pharmacological interventions will provide the most effective strategy for reducing the risk of recurrent CVD events. Here, we review risk prediction and non-invasive non-pharmacologic and pharmacologic approaches to mitigate residual coronary artery disease risk.

Introduction

Despite many advances in cardiovascular medicine, cardiovascular disease (CVD) remains the leading cause of mortality worldwide. In 2016, nearly 18 million people died of cardiovascular diseases globally. Of these, 9.4 million were caused by coronary artery disease (CAD). In addition, the burden of mortality from CAD is spreading beyond traditional high-income areas [1].

In addition to this burden of mortality, CVD also generates a high economic cost. In the USA, the direct cost of CVD was $213.8 billion in 2014–2015. This is over double the cost from 1996 to 1997, of $103.5 billion. Although risk factor modification, widespread use of primary revascularization, and secondary prevention strategies have helped reduce cardiovascular mortality and morbidity in recent times, these costs are anticipated to continue to precipitously increase. A further doubling of the total economic cost of CVD is predicted between 2015 and 2035, from $318 billion to $749 billion [2].

Recurrent risk prediction

The recently revised ACC/AHA ASCVD risk calculator is widely used and is intended for use in predicting risk of a first cardiovascular event [3]. However, this tool is commonly used in a secondary prevention setting as well, with a relative lack of specific risk calculation strategies in this cohort. Recently, a clinical tool for calculating recurrent CVD risk has been developed in TRS-2oP (Table 1) [4•]. It has been validated in a trial setting, and recently has been shown to demonstrate good correlation in multiple cohorts. It is particularly useful in identifying patients at high risk [5–7].

Diet

Previous data suggests that a "higher quality" diet, rich in fruits, vegetables, and whole grains, and lower in alcohol and trans-fats, conferred benefit in prevention of major chronic diseases, including CAD [8, 9]. As such, this strategy is supported by the 2013 ACC/AHA guideline on lifestyle management to reduce CVD risk [10].

Results of the DART trial also suggest increased intake of fatty fish conferred benefit in terms of reducing all-cause mortality in men post-myocardial infarction [11]. However, results of the follow-up trial, DART-2, did not replicate these findings, and indeed showed a trend towards increased mortality in a subgroup taking fish oil supplements [12].

Other studies have demonstrated that a "Mediterranean" diet, lower in dietary fat overall and relatively higher in oleic and alpha-linolenic acids, confers benefit in prevention of cardiovascular disease [13, 14] The PREDIMED study is awaited to objectively assess this diet in secondary prevention [15].

Other dietary interventions for health have come to public attention recently, notably intermittent fasting and its variations. A recent randomized, crossover trial has demonstrated benefit of the fasting-mimicking diet (FMD) in reducing numerous cardiovascular risk markers, including

Table 1. Clinical variables included in the TRS-2oP score

Clinical variable	Hazard ratio (95% CI)	Points allocated
CHF	2.03 (1.68–2.46)	1
Prior CVA	1.83 (1.39–2.4)	1
Hypertension	1.61 (1.34–1.93)	1
Diabetes mellitus	1.49 (1.27–1.75)	1
Current smoking	1.47 (1.23–1.75)	1
Prior CABG	1.44 (1.2–1.73)	1
Age > 75	1.4 (1.11–1.75)	1
Renal dysfunction*	1.36 (1.12–1.65)	1
Peripheral vascular disease†	1.36 (1.13–1.64)	1

Bohula et al. 2016
*Renal dysfunction defined as eGFR < 60 mL/min/1.73 m^2
†Peripheral vascular disease defined by clinical history of claudication, ankle-brachial index < 0.85, previous revascularization or amputation

BMI, systemic blood pressure, total and low-density lipoprotein (LDL) cholesterol, triglycerides, and C-reactive protein [16].

Epidemiologic studies link the consumption of whole food plant–based diets with improvements in CVD risk factors [17–20]. Analysis of trials comparing plant-based strategies for weight loss suggests plant-based dietary strategies to reduce recurrent CVD risk [21]. Plant-based choices may also be linked to an overall improvement in health-related behaviors, separately conferring benefit.

Indeed, older studies suggested "intensive lifestyle changes," involving a combination of "whole-food," vegetarian diets, exercise, stress management, and medications, had been suggested to halt or even reverse prevalent CAD [22–27].

Physical activity

Physical activity confers a plethora of health benefits. Comprehensive cardiac rehabilitation programs help deliver these benefits to patients with symptomatic CAD, as well as providing education and resources. Individual trials demonstrated reduced hospital admissions and potentially reduced all-cause mortality [28–31]. Recently, Cochrane reviewers found that exercise-based CR reduces cardiovascular mortality in comparison with a no-exercise control (risk ratio (RR) 0.74, 95% CI 0.64 to 0.86) among individuals referred after myocardial infarction. The risk for hospital admission was decreased in CR groups (RR 0.82, 95% CI 0.70 to 0.96) [32].

Exercise also directly modifies CV risk factors. One study demonstrated reductions in small LDL-cholesterol and overall concentration of LDL-cholesterol in a high-volume, high-intensity treatment group [33]. High-volume, high-intensity exercise is also associated with increased high-density lipoprotein (HDL) efflux as measured by global radiolabelled efflux [34].

Recent data also suggests that physical activity independently confers a survival advantage for those with CAD. High-volume physical activity (≥ 150 min of moderate-intensity or ≥ 60 min of vigorous activity per week) was associated with a 36% lower all-cause mortality risk versus inactivity (HR 0.64, 95% CI 0.50 to 0.83). A change from inactive to high physical activity conferred a 32% (HR 0.68, 95% CI 0.47 to 0.97) lower risk of cardiovascular mortality [35].

The 2018 US Physical Activity Guidelines recommends that adults should do > 150–300 min/week of moderate-intensity, or 75–150 min/week of vigorous-intensity aerobic physical activity, or an equivalent combination [36].

Smoking

The 1964 Surgeon General's report on the health effects of smoking clearly articulated the CVD risks of smoking [37]. The 1983 Surgeon General's report further outlined evidence that multiple pathogenic pathways are activated by smoking, including endothelial dysfunction, inflammation, lipid alterations, increase in prothrombotic state, and myocardial oxygen supply-demand mismatch [38]. Recent smoking statistics from the CDC give overall prevalence rates of 17.5% and 13.5% in men and women in the general population [39].

A recently published review of three decades of data from the Framingham cohort demonstrated mitigated but persistently elevated cardiovascular risk in smokers across all decades of follow-up, despite improvements in risk factor modulation across that time [40].

Smoking cessation confers a significant protective effect in those with CAD and recent acute coronary syndrome. In those with known CAD, observational studies suggest a pooled reduction in overall mortality of up to 35% [41, 42]. In follow-up analyses of OASIS-5, patients post-ACS who successfully quit were 43% less likely to experience myocardial infarction (MI) at six months (95% CI 0.36 to 0.89, $P = 0.0145$) [43].

Low-density lipoprotein cholesterol

Circulating cholesterol levels were linked to atherosclerotic coronary artery disease since the original Framingham Heart Study in 1957. Over time, low-density lipoprotein cholesterol (LDL-C) levels emerged as being directly related to elevated coronary artery disease risk [44–49]. More recently, LDL particle number (LDL-P) has been observed to be strongly associated with primary and secondary CAD risk compared with conventional LDL-C measurements [50, 51]. Particle number may also more accurately predict risk in those with discordant LDL-P and LDL-C, such as in type 2 diabetes and metabolic syndrome [52, 53]. Also, recent data suggest the subfractions of small dense LDL and oxidized LDL particles are proposed as being more atherogenic than others [54, 55].

HMG-CoA reductase inhibitors (statins)

Statin medications have long been used to reduce circulating LDL-C levels via inhibition of HMG-CoA reductase, the rate-limiting enzyme for cholesterol

Table 2. Event rates in contemporary secondary prevention trials

Medication class	Trial	Recruitment period	Primary outcome* rate (control)	Primary outcome rate (intervention)	Median follow-up (years)	Approximated annual event rate† (placebo)
Statins	TNT	April 1998–Dec 1999	10.90%	8.70%	4.9	2%
	PROVE-IT TIMI-22	Nov 2000–Dec 2001	26.30%	22.40%	2	13%
	LIPID‡	Apr 1990–Sept 1992	14.10%	11.00%	6	2%
Ezetimibe	IMPROVE-IT§	2005–2010	3.47%	3.27%	7	3%
PCSK9 monoclonal antibodies	ODYSSEY	Nov 2012–Nov 2015 (main cohort)	11.10%	9.50%	2.8	4%
	FOURIER	Feb 2013–June 2015$	11.30%	9.80%	2.16	5%
	SPIRE-1,2¶	Oct 2013–Nov 2016	3.16%	3.59%	0.8	3.16%
Eicosapentaenoic acid	REDUCE-IT**	Nov 2011–Aug 2016	19.30%	25.50%	4.9	4%
	JELIS**	1996–1999	10.70%	8.70%	4.6	2%
Niacin	HPS2 THRIVE††	Apr 2007–July 2010	13.70%	13.20%	3.9	4%
	AIM HIGH	2006–2010	16.20%	16.40%	3	5%
SGLT2 inhibitors	EMPA-REG	Sept 2010–Apr 2013	12.10%	10.50%	3.1	4%
	CANVAS‡‡	Dec 2009–Mar 2011	3.15%	2.69%	2.4	3.15%
	DECLARE-TIMI58	2013 onwards	9.40%	8.80%	4.2	2%
GLP-1 agonist	SUSTAIN-6	Feb 2013–Dec 2013	8.90%	6.60%	2.1	4%
	LEADER	Sept 2010–April 2012	14.90%	13.00%	2.8	5%
CETP inhibitors	dalOUTCOMES	April 2008–July 2010	8.30%	8.00%	2.6	3%
	ACCELERATE	Oct 2012–Dec 2013	12.80%	12.90%	2.16	6%
	REVEAL	Aug 2011–Oct 2013	11.80%	10.80%	4.1	3%
P2Y12 inhibitors	DAPT	Aug 2009–July 2011	5.90%	4.30%	2.5	2%
	PLATO§§	Oct 2006–July 2008	11.70%	9.80%	1	12%
	TRITON-TIMI38§§	Nov 2004–July 2007	12.10%	9.90%	1.25	10%
	PEGASUS-TIMI54¶¶	Oct 2010–May 2013	9.04%	7.81%	2.75	3%
Direct oral anticoagulants	COMPASS***	Mar 2013–May 2016	5.40%	4.1%	1.9	3%

Table 2. (Continued)

Medication class	Trial	Recruitment period	Primary outcome* rate (control)	Primary outcome rate (intervention)	Median follow-up (years)	Approximated annual event rate† (placebo)
Anti-inflammatory agents	CANTOS[¶, †††]	Apr 2011–Mar 2014	4.50%	3.86%	3.7	4.50%
	CIRT[¶]	Apr 2013–Mar 2018	4.31%	4.13%	2.3	4.30%

*Primary outcome as a combined rate of major adverse cardiovascular events, unless otherwise stated
†Approximated annual event rate: reported primary outcome rate/median follow-up
‡Primary outcome in LIPID was all-cause mortality
§Kaplan-Meier event rate at median follow-up listed for IMPROVE-IT
¶Event rates originally reported as events per 100 patient-years; approximated to annual event rate here
**Established cardiovascular disease subgroups listed
††Primary outcome in HPS2-THRIVE was first major cardiovascular event
‡‡Event rates originally reported as events per 1000 patient-years; approximated to annual event rate here
§§Event rates reported at follow-up duration listed
¶¶Intervention group taken as pooled ticagrelor group in PEGASUS-TIMI 58
***Intervention group taken as rivaroxaban plus aspirin for COMPASS
†††Intervention rate reported for 150-mg subgroup under intervention group rates

synthesis. They were known to reduce cardiovascular morbidity and mortality in stable coronary artery disease, and their secondary prevention benefit in reducing recurrent CAD events and mortality was demonstrated in multiple randomized controlled clinical trials, including MIRACL, PROVE-TIMI 22, and IDEAL trials (Table 2). PROVE-TIMI 22 and IDEAL also suggested superiority of higher intensity therapy in reducing residual risk [56–58]. As such, LDL-C lowering with statins is a cornerstone of CVD risk reduction.

Ezetimibe

Ezetimibe acts via inhibition of gastrointestinal absorption of dietary cholesterol. The IMPROVE-IT compared the combination of ezetimibe with simvastatin against simvastatin monotherapy among individuals with ASCVD. At a median of 6 years, there were decreased rates of the combined primary endpoint of cardiovascular death, nonfatal myocardial infarction (MI), unstable angina requiring readmission, and revascularization or nonfatal stroke (Kaplan-Meier event rate of 32.7% in the treatment group vs. 34.7%; HR 0.93 (95% CI 0.89–0.99, $p = 0.016$)). Notably, similar effects were seen with rates of fatal MI (14.8% vs. 13.1%, $p = 0.002$) and nonfatal MI (14.4% vs. 12.8%) [59••]. Recently, subgroup analyses among diabetics demonstrated greater absolute risk reduction with ezetimibe and potentially greater relative risk reduction among diabetics younger than 75 years [60].

PCSK9 monoclonal antibodies

ODYSSEY Outcomes studied alirocumab, a humanized monoclonal antibody inhibitor of PCSK9, in patients with recent (1–12 months) acute coronary syndrome on maximal statin therapy but with persistent LDL-C > 70 mg/dL. Primary outcome was defined as a composite of major adverse cardiac events (MACE); the median follow-up was 2.8 years. The overall rate of MACE was 11.1% in the placebo group and 9.5% in the treatment group (ARR 1.6%). Rates of CAD events were 14.3% vs. 12.7% (ARR 1.6%, HR 0.88 [95% CI 0.81–0.95]) and major CAD events were 8.4% vs. 9.5% (ARR 1.1%, HR 0.88, 95% CI 0.8–0.96). Notably, there was a greater treatment effect regarding MACE, CAD death, CV death, and all-cause death in patients with baseline LDL-C > 100 mg/dL [61, 62]. Furthermore, an analysis pooling total recurrent incident events (instead of only considering first events) demonstrated even greater clinical benefit (i.e., ~ twofold reduction in total CVD events) with alirocumab versus placebo [63•].

FOURIER evaluated evolocumab, another monoclonal antibody targeting PCSK9, in patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease on statin therapy but with LDL-C > 70 mg/dL. Primary outcome was a composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. This was seen in 9.8% of the treatment group, and 11.3% of the placebo group (ARR 2%, $p < 0.0001$). Absolute benefit was greater in patients with significant residual CAD, recent MI and multiple prior MIs, and with higher baseline high-sensitivity C-reactive protein (hs-CRP) [64, 65].

In the 2018 ACC/AHA Cholesterol Guidelines, PCSK9 monoclonal antibodies are recommended to achieve LDL-C > 50% lowering to < 100 mg/dL when "very high risk" ASCVD is present [66].

PCSK9 siRNA

Another avenue for manipulation of the PCSK9 pathway is via small interfering RNA molecules, notably inclisiran. ORION-1 was a phase II trial that evaluated inclisiran dosed bi-annually in patients with LDL-C levels above target despite statin therapy, of high CVD risk. The average reductions in LDL-C were significantly greater after a single dose of inclisiran (27.9–41.9% reduction) than those with placebo (2.1% increase) [67]. More recent studies demonstrated the safety and durability of effect in patients with type 2 diabetes [68].

PCSK9 gene editing

In recent years, it has been demonstrated that clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) system–mediated genetic editing effectively and efficiently induced loss-of-function mutations in endogenous PCSK9. In one study, there was response within days to administration of CRISPR-Pcsk9 adenoviruses in hepatocytes, with resultant 35–40% reduction in total cholesterol compared with the control group. This reduction in LDL-C was comparable with rates seen in PCSK9 knockout mice [69, 70].

PCSK9 vaccination

Another novel method of PCSK9 modulation is via PCSK9 antibody formation. A recent study in a male, ApoE-deficient mouse model demonstrated durable formation of anti-PCSK9 antibodies, resulting in decreased PCSK9-LDLR interactions and resultant lower plasma total cholesterol, VLDL-cholesterol, and triglycerides. However, there was less effect on LDL-C levels [71].

Bempedoic acid

Bempedoic acid is a first-in-class small-molecule adenosine triphosphate (ATP)-citrate lyase inhibitor that acts upstream of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase to inhibit cholesterol biosynthesis and increase LDL receptor expression. Phase II trials had demonstrated its tolerability and efficacy in lowering LDL-C and hs-CRP levels [72–75]. CLEAR Tranquillity assessed bempedoic acid with ezetimibe in CVD patients intolerant of high-intensity statins. Results demonstrated that bempedoic acid with ezetimibe decreased mean LDL-cholesterol concentration by − 28.5% (95% CI − 34.4%, − 22.5%; $p < 0.001$) compared with ezetimibe alone at 12 weeks [76].

Triglycerides

Epidemiological studies have suggested that triglycerides (TG) are associated with residual CVD events independent of achieved LDL-C concentrations. Elevated TG levels are also elevated levels of remnant circulating cholesterol particles, which are also present in triglyceride-rich lipoproteins. Many epidemiological cohort studies support TG as an independent risk factor for ASCVD, and recent meta-analysis suggests dose-dependent increases in CVD risk and mortality with increasing TG levels. In addition, genetic analyses have suggested a causal link between TG-rich lipoprotein concentrations and CVD risk [77–80]. Recent genetic analyses suggest that the correlation of TG-rich lipoprotein with CAD risk may be explained by apolipoprotein B, the primary determinant of atherogenic lipoproteins including LDL [81, 82].

Eicosapentaenoic acid

Given the plausibility that omega-3 fatty acids may mediate some of the CVD risk reduction with consumption of fatty fish, a number of studies have evaluated the relationship between pharmacologic omega-3 fatty acids and CVD risk. Omega-3 fatty acid supplements are primarily comprised of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), but have largely not shown an association of CVD risk reduction [83].

The JELIS trial examined high-dose EPA with statin against statin monotherapy and demonstrated an ARR of 0.7% and RRR of 19% in major coronary events, with effect significant only in those with baseline CAD [84]. This was further supported by the REDUCE-IT trial, which assessed reduction in MACE with supplementation of 4 g/day EPA. It showed an ARR of 6.2% and RRR of 25% in primary outcome of MACE for the secondary prevention cohort [85••]. Whether the apparent treatment effect for EPA is explained only by reduction in TG-rich lipoproteins or by other potential cardioprotective pleiotropic effects requires further study.

The pending STRENGTH trial will examine whether a proprietary blend of omega-3 carboxylic acids in high-risk primary and secondary prevention will lower CVD event risk [86].

Lipoprotein(a)

Lipoprotein(a) (Lp(a)) consists of an apolipoprotein B–containing LDL-like particle linked to a plasminogen-like glycoprotein apo(a). Observational studies showed that Lp(a) levels are associated with higher risk of incident cardiovascular disease in primary prevention settings [87, 88].

AIM-HIGH, JUPITER, and LIPID trials all demonstrated that baseline Lp(a) levels were significantly associated with risk of future CAD events. A meta-analysis showed that those with Lp(a) levels in the highest quintile increased risk of MACE by 40% (OR 1.4, 95% CI 1.15–1.71, $p = 0.001$). This analysis suggested the risk only remained significant with baseline elevated LDL-C (> 130 mg/dL) [89–93]. However, genome-wide association studies have shown *LPA* genetic variants are associated with recurrent CVD risk, independent of levels of LDL-C [94•].

A recent genetic analysis assessed by how much Lp(a) would theoretically need to be reduced in order to produce a meaningful level of risk reduction. It suggested a reduction of 102 mg/dL would achieve similar levels of risk reduction as reducing LDL-C by 39 mg/dL. It also suggested reductions of 50 mg/dL and greater were associated with > 10% estimated risk reductions in the short term [95•].

One issue with including Lp(a) in risk-reducing strategies is the current lack of direct therapies. Lp(a) levels are variably affected by other lipid-lowering interventions. Indeed, high-dose, high-potency statins have been associated with increased Lp(a) levels [96, 97]. Other interventions have been shown to reduce Lp(a) levels, such as niacin, IL-6 antagonists, and PCSK9 inhibitors [98–100].

Therapies that are under investigation as directed therapies to reduce Lp(a) include antisense nucleotides to apo(a). IONIS-APO(a)Rx phase I and II trials have investigated antisense oligonucleotides and have suggested reductions in circulating concentration of Lp(a) of up to 90% with no apparent acute side effects. Phase III trials evaluating the effect of this reduction on cardiovascular outcomes are awaited [101, 102].

Diabetes mellitus

Diabetes mellitus is one of the most well-established CVD risk factors. However, the DCCT trial demonstrated that intensive blood glucose control did not reduce risk of macrovascular complications. The ABCD and UKPDS studies some years later corroborated this, and did not detect significant changes related to cardiovascular mortality with improvements in glycemic control [103, 104].

Since data suggested that use of rosiglitazone may increase CV risk, cardiovascular outcomes trials (CVOTs) have been required for all new glucose-lowering agents. Recent CVOTs that demonstrated safety but not protective benefit include SAVOR-TIMI 53 (saxagliptin), EXAMINE (alogliptin), EXSCEL (exanetide), ELIXA (lixisenatide), and TOSCA.IT (pioglitazone plus sulfonyureas) [105–110].

There are now five CVOTs to date that, however, demonstrated benefit in reducing CV risk in diabetic patients. These include SUSTAIN-6 and LEADER, which evaluated semaglutide and liraglutide of the GLP-1 agonist class, and EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58, which evaluated empagliflozin, canagliflozin, and dapagliflozin of the SGLT2 inhibitor class [111, 112••, 113••, 114, 115].

GLP-1 receptor agonists

SUSTAIN-6 CVOT examined semaglutide. Overall, 60% of participants had cardiovascular disease at baseline. After a median of 2.1 years, primary outcome of MACE occurred in 6.6% of the semaglutide group and 8.9% in the placebo group (HR 0.74, 95% CI 0.58 to 0.95). It did not demonstrate benefit in reducing risk of cardiovascular death or nonfatal MI [111].

The LEADER CVOT examined liraglutide. It demonstrated benefit in reducing rates of MACE (13.0% vs. 14.9%; HR 0.87, 95% CI 0.78–0.97). In addition, there were significantly lower rates of cardiovascular and all-cause death [112••].

SLGT2 inhibitors

EMPA-REG OUTCOMES was the first CVOT to demonstrate cardiovascular benefit with glucose-lowering agents. It evaluated empagliflozin. Over 75% of patients had established CAD, with ~ 50% having prior MI. Rates of MACE were significantly lower in the treatment group (10.5% versus 12.1%; HR 0.86, 95% CI 0.74–0.99). There was also significant difference in the rates of hospitalization for heart failure and all-cause mortality. The effect of the empagliflozin was seen early on Kaplan-Meier event curves [113••].

The CANVAS CVOTs assessed canagliflozin. They found a significant reduction in MACE in the treatment group compared with placebo (26.9 vs. 31.5

participants with an event per 1000 patient-years; HR 0.86, 95% CI 0.75 to 0.97; $P = 0.02$ for superiority). Rates of hospitalization for heart failure were again significantly reduced. However, they noted an increased risk of fracture (15.4 vs. 11.9 events per 1000 patient-years; HR 1.26; 95% CI 1.04 to 1.52) and lower limb amputation (6.3 vs. 3.4 events per 1000 patient-years, HR 1.97; 95% CI 1.41 to 2.75) in the treatment group [114].

DECLARE-TIMI 58 assessed cardiovascular outcomes for dapagliflozin. It did not find a significant difference in the MACE rate in the general cohort (8.8% vs. 9.4% in placebo; HR 0.93, 95% CI 0.84–1.03; $P = 0.17$), or in those with prior CAD. However, it did corroborate lower risk of hospitalization for heart failure. It did not find significant increases in rates of lower limb amputation or fracture [115].

A 2018 ACC Expert Consensus document recommends initiation of either of a GLP-1 receptor agonist or SGLT2 inhibitor in patients with type 2 diabetes mellitus, in addition to metformin and other risk factor modification strategies. Liraglutide is the preferred agent of the GLP-1 RA class, and empagliflozin is the preferred agent of the SLGT2 inhibitors (SGLT2i) class [116].

High-density lipoprotein cholesterol

Epidemiologic data suggests HDL-C concentrations are inversely related to cardiovascular risk. However, recent analyses demonstrated that increases in HDL-C caused by genetic polymorphisms do not confer a risk advantage in preventing future myocardial infarction, implying lack of a causal relationship [117].

Previously, AIM-HIGH assessed addition of niacin to a high-intensity statin regime. It demonstrated no additional risk reduction benefit despite significant increases in HDL-C [118]. Later, HPS2-THRIVE assessed the risk reduction effects of niacin in a heterogeneous cohort of high-risk patients with CVD. Again, there was no risk reduction benefit seen despite increased serum HDL-C [119].

Additional evidence against HDL-C in preventing cardiovascular events was suggested from dalOUTCOMES trial, which assessed the cholesterol ester transfer protein (CETP) inhibitor, dalcetrapib. Despite a 31% increase in HDL-cholesterol levels in their treatment group with no difference seen in rates of the primary endpoint of MACE [120].

ACCELERATE assessed another CETP inhibitor, evacetrapib, in patients with recent ACS, known ASCVD, or diabetes mellitus. Despite a marked increase in HDL-C (133.2% vs. 1.6%), there was no difference in rates of primary endpoint of MACE (12.9% vs. 12.8%; HR 1.01, 95% CI 0.91 to 1.11; $P = 0.91$) [121].

The REVEAL trial assessed anacetrapib in patients with known ASCVD on high-intensity statins. Mean HDL-C levels increased in the treatment group by 43 mg/dL (104% vs. placebo), and non-HDL-C notably also declined by 17 mg/dL (– 18% vs. placebo). The median follow-up was 4.1 years. There was ARR of 1% in the first occurrence of MACE (10.8% vs. 11.8%; RR 0.91; 95% CI 0.85–0.97). Overall, it is thought the trial effect is driven by the reduction in non-HDL-C rather than increase in HDL-C [122•].

Whether other properties of HDL, such as reverse cholesterol transport, may influence ASCVD risk requires further study. Observational data in patients

without cardiovascular disease demonstrated that those with the highest quartile of HDL-cholesterol efflux capacity (a measure of reverse cholesterol transport) had a 67% reduction in composite ASCVD rates compared with the lowest quartile at 9.7 years of follow-up [123].

Platelets and thrombosis

The final common pathway for a CAD event is coagulation and thrombosis. The antiplatelet agent aspirin is known to reduce mortality in acute coronary syndromes [124]. Dual antiplatelet therapy, combining aspirin with P2Y12 inhibitors, is critical in maintaining stent patency after PCI. Recently, the DAPT and PEGASUS TIMI-54 trials have demonstrated longer durations of DAPT beyond 1 year of treatment reduce risk of stent thrombosis and MACE [125]. In PEGASUS TIMI-54, there was a slight but significant increase in the rates of major bleeding only in the higher dose ticagrelor group [126]. More recent follow-up analyses of this trial have demonstrated this benefit persists at 5 years in the trial setting, with slight attenuation of bleeding risk as time progressed [127••]. Scores, such as the DAPT score, may identify candidates for a more prolonged duration of P2Y12 inhibition [128•].

Oral vitamin K antagonists (VKORs) help reduce residual cardiovascular risk in patients with myocardial infarction, at a cost of increased bleeding rates. However, direct acting oral anticoagulants (DOACs) have been developed with reduced bleeding risk compared with VKORs. COMPASS investigated the benefit and safety of rivaroxaban 2.5 mg twice daily in secondary prevention. The rivaroxaban plus aspirin group demonstrated the lowest MACE event rate (4.1%) compared with rivaroxaban alone (4.9%) and aspirin alone (5.4%). Rivaroxaban plus aspirin compared with aspirin alone had a HR of 0.76 (95% CI 0.66–0.86; $p < 0.001$). Major bleeding occurred more in the combination group than with aspirin alone, but there were no significant differences in rates of fatal bleeding [129]. Recently, the FDA approved the use rivaroxaban 2.5 mg twice daily in adjunct to aspirin for secondary prevention; this strategy has not yet been incorporated into professional guidelines [130].

Inflammation

Manipulating inflammation to reduce ASCVD risk has been proposed based on epidemiologic and basic biomedical investigations [131]. Elevated concentrations of hs-CRP, an inflammatory biomarker, are associated with elevated CVD risk independent of established cardiovascular risk factors [132].

Recently, the CANTOS trial tested the clinical efficacy of this strategy in humans using canakinumab, a monoclonal antibody targeting interleukin-1 beta (IL-1B). IL-1B is a central cytokine in the interleukin-6 (IL-6) pathway, which has been suggested by genetic analyses to be causative in atherosclerosis, and high levels are associated with increased risk of cardiovascular events [133–135].

CANTOS evaluated patients with a history of prior MI and hs-CRP level of > 2 mg/dL. All treatment groups experienced significant reductions in hs-CRP levels. After a median of 3.7 years, there was a significant difference in the rates of primary endpoint of MACE in the 150 mg (HR 0.85, 95% CI 0.74–0.98; $p =$

0.021) and 300-mg groups (HR 0.86, 95% CI 0.75–.099; $p = 0.031$). There was an increased rate of deaths related to infection in the pooled treatment groups [136•]. However, FDA recently indicated that current evidence for canakinumab is insufficient to support a label for CVD risk reduction [137]. The CIRT trial did not observe an improvement in CVD risk among a similar population with low-dose methotrexate [138]. These data indicate that specific inflammatory pathways, such as IL-1B/IL-6, may be more favorable for risk modulation than others.

Conclusion

Despite increasingly durable and intensive LDL-C-lowering therapies, significant residual risk remains after people experience cardiovascular events. Strategies to improve the delivery and adherence of lifestyle modification have an opportunity to address this risk. Additionally, orthogonal strategies to lower recurrent CVD risk among key subgroups can help facilitate tailored therapies to optimize medical strategies to reduce recurrent CVD risk.

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Compliance with Ethical Standards

Conflict of Interest
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Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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