Strategies for the Secondary Prevention of Atherosclerotic Cardiovascular Disease

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Abstract

Patients with atherosclerotic cardiovascular disease (ASCVD), such as those with a history of MI or stroke, are at high risk for morbidity and mortality associated with future cardiovascular events. Ideal management of these patients requires a multifactorial strategy for risk factor mitigation and prevention of additional cardiovascular events. Traditional management of secondary prevention patients involves lipid-lowering with statins, blood pressure control, and anti-platelet treatment. Several additional targets have been identified to optimize the secondary prevention of ASCVD, such as further lipid control, inflammation management, lifestyle and weight optimization, strict diabetes control, use of β-blockers, use of renin–angiotensin–aldosterone system inhibitors, vaccinations, and additional considerations of anti-thrombotic therapies. This review will describe the interventions associated with these targets, as well as the relevant research and indications for these therapies.

Keywords

Atherosclerotic cardiovascular disease, MI, stroke, lipids, triglycerides, inflammation, diabetes

Received: June 25, 2024 **Accepted:** February 26, 2025 **Citation:** *US Cardiology Review* 2025;19:e11. **DOI:** https://doi.org/10.15420/usc.2024.33
Disclosures: SSV has received research grants from the National Institutes of Health, National Institute for Health and Care Research (UK), Department of Veterans Affairs, Tahir and Jooma Family and Asharia Family. All other authors have no conflicts of interest to declare.
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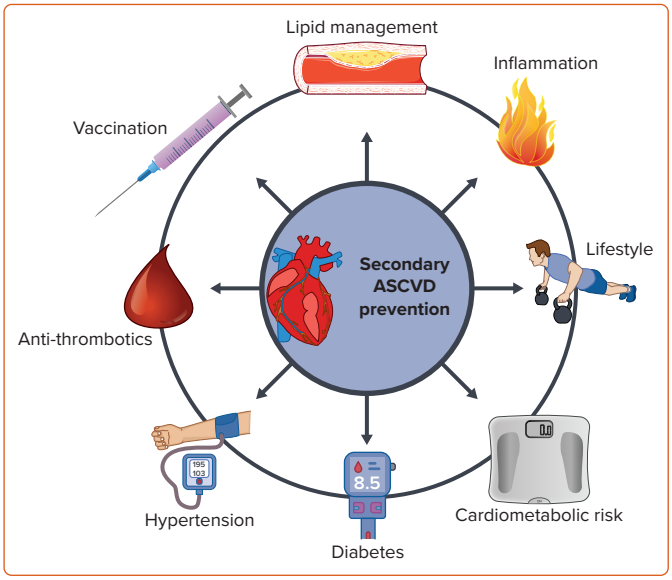
Central Illustration: Secondary Management of Established Atherosclerotic Cardiovascular Disease



ASCVD = atherosclerotic cardiovascular disease.

Despite improvements in risk factor management and the care of patients with atherosclerotic cardiovascular disease (ASCVD), the global burden of ASCVD remains high and exceedingly costly.[1,2] Notably, patients with established ASCVD, such as those with prior MI or stroke, are at high risk of additional future cardiovascular events.[3–6] With this in mind, attention focuses on further strategies for ASCVD prevention in addition to more conventional proven measures, such as blood pressure control, lipid-lowering with statins, and treatment with aspirin.

This review will survey the guidelines associated with and recent research on under-recognized or under-managed targets of secondary prevention of ASCVD, with a special focus on lipid management, systemic inflammation, lifestyle interventions, weight management, diabetes management, use of β-blockers, use of renin–angiotensin–aldosterone system (RAAS) inhibitors, appropriate vaccinations, and anti-thrombotic therapies (*Table 1*).[7–11]

Lifestyle Interventions

Diet

Randomized controlled trials (RCTs) have shown plant-based or Mediterranean diets (i.e. a high intake of fruits, vegetables, and whole grains, with an emphasis on unsaturated fats over saturated fats and lean proteins over red meat) to be effective in secondary prevention of

Table 1: Selected Guidelines for Secondary Prevention of Atherosclerotic Cardiovascular Disease

Intervention	2023 AHA/ACC Chronic Coronary Disease Guidelines[7] (Recommendation/Class)	2021 ESC ASCVD Prevention Guidelines[8] (Recommendation/Class)	2021 and 2022 Canadian Guidelines[10,11] (Recommendation/Level)
Lifestyle			
Diet	• Prioritize plants and lean proteins (class 1) • Reduce saturated fats and refined carbohydrates (class 2a)	• Mediterranean or similar diet, increase plant intake (class 1) • Reduce saturated fats, free sugar, salt (class 1)	• Mediterranean or similar diet with high plant intake
Physical activity	• At least 150 min/week of moderate-intensity or 75 min/week of high-intensity exercise in patients without contraindications (class 1) • Resistance training at least 2 days/week in patients without contraindications (class 1)	• At least 150 min/week of moderate-intensity, 75 min/week of high-intensity exercise, or as much as health conditions will allow (class 1) • Resistance exercise at least 2 days/week (class 1)	• At least 150 min/week of moderate- to high-intensity aerobic activity
Cardiac rehabilitation	• Class 1	• Class 1	
Sexual activity	• Resume after evaluation of exercise capacity and type of sexual activity (class 2a) • Regular physical activity and cardiac rehabilitation to reduce risks (class 2a) • Use of phosphodiesterase-5 inhibitors with nitrates (class 3: harm)		
Mental health	• Screen all patients and treat if indicated (class 2a)	• Increase support for patients with known mental health disorders to improve treatment adherence (class 1) • Assess stressors and psychosocial health and refer to therapy as indicated (class 2a)	
Smoking cessation	• Regular evaluation for tobacco use, counseling for smoking cessation, behavioral or pharmacological interventions if indicated (class 1) • Prioritize varenicline over bupropion or nicotine replacement therapy (class 2a) • Consider short-term use of e-cigarettes for smoking cessation, but weigh unclear risks of long-term use (class 2b)	• Smoking cessation (class 1) • Use behavioral counseling, nicotine replacement therapy, varenicline, or bupropion to support smoking cessation (class 2a)	• Smoking cessation
Substance use	• Routine substance use screening and counseling (class 1) • Limit alcohol consumption (≤1 drink/day for women, ≤2 drinks/day for men) (class 2a)	• Decrease alcohol consumption to <100 g/week (class 1)	• Limit alcohol consumption to moderate
Weight			
Lifestyle	• Routine assessment of BMI, counseling on diet, lifestyle, weight loss for patients with BMI >25 kg/m^2 (class 1)	• Weight loss counseling for patients who are overweight or obese (class 1)	
GLP-1-RA	• Patients with BMI ≥30 kg/m^2 or BMI 25–29.9 kg/m^2 with weight-related comorbidity who have not met goals with lifestyle interventions (class 2a)		
Bariatric surgery	• Patients with BMI ≥40 kg/m^2 or BMI 35–39.9 kg/m^2 with a weight-related comorbidity who have not met goals with lifestyle or pharmacologic interventions (class 2a)	• Obese high-risk patients who have not maintained weight loss with lifestyle change (class 2a)	
T2D			
SGLT2I	• Class 1	• Class 1	• Strong
GLP-1-RA	• Class 1	• Class 1	• Strong
LDL-C Management			
Statin	• Highest intensity tolerated to achieve at least 50% decrease in LDL-C (class 1)	• Highest intensity tolerated to achieve LDL-C <1.42 mmol/l and at least 50% decrease from baseline (class 1)	• Highest intensity statin tolerated (strong)
Ezetimibe	• Very high-risk patients on maximally tolerated statin with LDL-C ≥1.81 mmol/l (class 2a) • Lower risk patients on maximally tolerated statin with LDL-C ≥1.81 mmol/l (class 2b)	• Patients on maximally tolerated statin with LDL-C ≥1.42 mmol/l (class 1)	• Patients on maximally tolerated statin with LDL-C ≥1.81 mmol/l (strong)

Table 1: Cont.

Intervention	2023 AHA/ACC Chronic Coronary Disease Guidelines[7] (Recommendation/Class)	2021 ESC ASCVD Prevention Guidelines[8] (Recommendation/Class)	2021 and 2022 Canadian Guidelines[10,11] (Recommendation/Level)
PCSK9 inhibitors	• Very high-risk patients on ezetimibe and maximally tolerated statin with LDL-C ≥1.81 mmol/l (class 2a)	• Patients on maximally tolerated statin and ezetimibe with LDL-C ≥1.42 mmol/l (class 1)	• Patients on maximally tolerated statin with or without ezetimibe with LDL-C ≥1.81 mmol/l (strong)
Bempedoic acid	• Patients on maximally tolerated statin, intolerant of ezetimibe and/or PSCK9 inhibitors with LDL-cholesterol ≥1.81 mmol/l (class 2b)		
Hypertriglyceridemia			
Fibrates	• Class 3: no benefit	• Patients on maximally tolerated statin with triglycerides >2.26 mmol/l (class 2b)	
Niacin	• Class 3: no benefit		
Icosapent ethyl	• Patients on maximally tolerated statin with LDL-C <2.59 mmol/l and persistent fasting triglycerides 1.69– 5.65 mmol/l after lifestyle modification (class 2b)	• Patients on maximally tolerated statin after lifestyle modifications with triglycerides >1.52 mmol/l (class 2b)	• Patients on maximally tolerated statin therapy with triglycerides >1.5 mmol/l (strong)
β-blockers			
	• Patients with uncontrolled HTN, reduced LVEF, or arrhythmia (class 1) • Reassess use 1 year after MI in patients without other primary indication (class 2b)	• Patients with reduced LVEF (class 1)	
RAAS Inhibitors			
	• Patients with HTN, T2D, reduced LVEF, chronic kidney disease (class 1) • Patients without other primary indication (class 2b)	• Patients with reduced LVEF, HTN, T2D (class 1)	
Inflammation			
Colchicine 0.5 mg daily	• Very high-risk patients on maximally tolerated guideline-directed medical therapy (class 2b)	• Consider, especially if other risk factors not well controlled (class 2b)	
Anti-thrombotic Agents			
Rivaroxaban 2.5 mg twice daily	• With daily aspirin in patients without indication for therapeutic anti-coagulation or dual anti-platelet therapy, considered high ASCVD risk and low-moderate bleeding risk (class 2a)	• With daily aspirin in patients at high risk of future ASCVD events and without high bleeding risk (class 2a) • With daily aspirin in patients at moderate risk of future ASCVD events and without high bleeding risk (class 2b)	
Vaccinations			
Influenza	• Class 1	• Class 1 (in 2019 chronic coronary guidelines)[9]	
Pneumococcal	• Class 2a		
COVID-19	• Class 1		

AHA/ACC recommendation classes: class 1, strong; class 2a, moderate; class 2b, weak; class 3: no benefit or class 3: harm. ESC recommendation classes: class 1, recommended/indicated; class 2a, should be considered; class 2b, may be considered; class 3, not recommended. AHA/ACC = American Heart Association/American College of Cardiology; ASCVD = atherosclerotic cardiovascular disease; ESC = European Society of Cardiology; GLP-1-RA = glucagon-like peptide-1 receptor agonists; HTN = hypertension; LDL-C = LDL cholesterol; LVEF = left ventricular ejection fraction; PCSK9 = proprotein convertase subtilisin/kexin type 9; RAAS = renin–angiotensin–aldosterone-system; SGLT2I = sodium–glucose cotransporter 2 inhibitors; T2D = type 2 diabetes.

ASCVD.[12,13] For example, the CORDIOPREV study compared the Mediterranean diet with a low-fat diet for secondary prevention of ASCVD and found that the Mediterranean diet decreased risk of major adverse cardiovascular events (MACE; unadjusted HR 0.745; 95% CI [0.563–0.986]).[14] This result persisted despite adjustment for age, sex, family history, smoking, BMI, weight changes, LDL cholesterol measurements, and baseline pharmacotherapies.[14] The PREDIMED study in high-risk individuals without preexisting ASCVD compared the effect of the Mediterranean diet plus either olive oil or nuts with a reduced-fat diet demonstrated a similarly reduced incidence of MACE.[15] Therefore, the 2023 American Heart Association (AHA)/American College of Cardiology (ACC) guideline for patients with chronic coronary disease (CCD) recommends a plant-based diet with lean protein (class 1: strong) and recommends reducing saturated fat and refined carbohydrate intake (class 2a: moderate).[7]

Physical Activity

Physical activity improves cardiovascular risk through multiple mechanisms, including improvement of ASCVD risk factors, such as dyslipidemia, hypertension, obesity, and insulin resistance, along with decreased inflammation, improved endothelial function, and increased coronary collateral blood flow.[16]

Increased physical activity correlates with decreased all-cause mortality

Table 2: Weight Loss Associated with Available Glucagon-like Peptide-1 and Glucagon-like Peptide-1/Glucose-dependent Insulinotropic Polypeptide Receptor Agonists

Drug (Dose/Route)	Mean Weight Loss	Treatment Duration (Weeks)	FDA-approved for Weight Loss
Liraglutide (3.0 mg/daily injectable)[44]	8% (SD 6.7)	56	Yes
Semaglutide (2.4 mg/weekly injectable)[43]	14.8%	68	Yes
Semaglutide (7 mg/oral)[45]	0.9 kg	26	No
Semaglutide (14 mg/oral)[45]	2.3 kg	26	No
Semaglutide (50 mg/oral)*[46]	15.5% (SE 0.5)	68	No
Dulaglutide (1.5 mg/weekly injectable)[47]	3.0 kg†	36	No
Dulaglutide (4.5 mg/weekly injectable)[47]	4.6 kg†	36	No
Exenatide (2 mg/weekly injectable)[48]	4.1 kg (95% CI [2.9–5.3])†	52	No
Tirzepatide (5 mg/weekly injectable)‡[49]	15% (95% CI [14.7–15.9])	72	Yes
Tirzepatide (10 mg/weekly injectable)‡[49]	19.5% (95% CI [18.5–20.4])	72	Yes
Tirzepatide (15 mg/weekly injectable)‡[49]	20.9% (95% CI [19.9–21.8])	72	Yes

**Not an FDA-approved dosing of semaglutide, may not be available. †In individuals on background therapy for type 2 diabetes. ‡Tirzepatide is a dual glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide receptor agonist. FDA = Food and Drug Administration.*

and cardiovascular mortality.[17,18] Evidence supports that combined aerobic and resistance training improves outcomes, such as peak oxygen intake, upper and lower body strength, and fat loss, compared with aerobic training alone.[19,20]

The 2023 AHA/ACC CCD guideline recommends an exercise regimen of at least 150 minutes/week of moderate-intensity or 75 minutes/week of high-intensity exercise for patients with ASCVD without contraindications with resistance training at least 2 days/week (class 1).[7] For those with appropriate indications (recent MI, percutaneous coronary intervention, coronary artery bypass graft, history of angina, heart transplant, or spontaneous coronary artery dissection), exercise-based cardiac rehabilitation, either in-person or remote, is recommended at a class 1 level by the 2023 AHA/ACC CCD guideline, considering the decreased risks of cardiovascular death (risk ratio 0.74; 95% CI [0.64–0.86]) and MI (risk ratio 0.82; 95% CI [0.70–0.96]).[7,21]

Regarding sexual activity, which represents a form of moderate physical activity, data suggest an overall low risk of MI or sudden cardiac death in the general population, which is further decreased by greater levels of regular physical activity.[22] The 2023 AHA/ACC CCD guideline endorses resumption of sexual activity after evaluation of exercise capacity and the type of sexual activity in patients with ASCVD (class 2a) and additionally recommends regular physical activity and cardiac rehabilitation as a method to reduce the risks associated with sexual activity (class 2a).[7] Of note, sexual dysfunction can be common after ASCVD events and phosphodiesterase 5 inhibitors such as sildenafil should not be used with nitrates, because of the risk of hypotension.[7]

Mental Health

Both the European Society of Cardiology (ESC) and the AHA recognize the complex interplay between mental health and cardiovascular disease.[23,24] Depression after MI is associated with worse outcomes, with one meta-analysis demonstrating an OR of 2.71 (95% CI [1.68–4.36]) for cardiac death.[24–26] Depression negatively impacts ASCVD risk factors and can interfere with optimal ASCVD treatment and risk factor management.[23,24,27] Conversely, positive mental health behaviors and habits can be protective following MI, with decreased rates of cardiac readmissions noted for patients post-MI with baseline optimism (HR 0.92; 95% CI [0.86–0.98]).[23,28] The 2023 AHA/ACC CCD guideline recommends screening all individuals with ASCVD for mental health conditions and treating, either pharmacologically or non-pharmacologically, where appropriate.[7]

Smoking, Vaping and Alcohol Use

There is a well-established association between cigarette smoking and ASCVD. Exposure to cigarette smoke has a multitude of deleterious effects on the cardiovascular system, such as increases in heart rate and blood pressure, increased myocardial oxygen demand, endothelial cell damage, activation of inflammatory pathways, and prothrombotic effects.[29,30] These effects can be ameliorated by smoking cessation. For example, smoking cessation increased flow-mediated dilation after 1 year, indicating improvements in endothelial function.[31] The benefits of smoking cessation for secondary prevention of ASCVD have been repeatedly demonstrated, with reductions in all-cause mortality, cardiovascular death, MACE, risk of repeat MI, and non-fatal stroke.[32,33]

The 2023 AHA/ACC CCD guideline endorses regular evaluation for tobacco use, counseling for smoking cessation, and behavioral or pharmacological interventions to support cessation efforts (class 1).[7] Varenicline is preferred over bupropion or nicotine replacement therapy (class 2a recommendation), because trials have demonstrated its increased efficacy and no increased cardiovascular events despite initial concerns.[7] Of note, alcohol consumption and use of other substances have also been associated with increased ASCVD risk, and as such, limiting alcohol consumption has been suggested by both American and European guidelines: one or fewer drinks/day for women, two or fewer drinks/day for men and less than 100 g/week, respectively.[7,8]

Because of the relative newness of electronic cigarettes and vaping, there is minimal research available on the long-term cardiovascular effects of using these products. However, physiological studies have demonstrated adverse effects on the cardiovascular system similar to those conferred by traditional cigarettes, such as increased heart rate, blood pressure, oxidative stress, and endothelial damage.[34,35] Available data suggest that some of these effects may be less pronounced than those associated with traditional cigarettes, exemplified by one

prospective RCT demonstrating improvements in endothelial function and vascular stiffness after 1 month of switching from traditional cigarettes to electronic cigarettes.[35,36]

Ultimately, without long-term data on clinical outcomes and the observation that patients who start electronic cigarettes may use them long-term, it is difficult to quantify the long-term cardiovascular risks associated with these devices, but the evidence available does support minimizing exposure in patients with ASCVD. The 2023 AHA/ACC CCD guideline states that short-term use of electronic cigarettes to aid in smoking cessation may be appropriate, but it should be weighed against the unclear risks of long-term use (class 2b: weak).[7]

Weight Management: Bariatric Surgery and Glucagon-like Peptide-1 Receptor Agonists

Because of the clear association of body weight with ASCVD risk factors and outcome benefits seen with weight loss, the 2023 AHA/ACC CCD guideline recommends routine assessment of BMI and counseling on diet, lifestyle, and goals for weight loss in any patients considered overweight (BMI 25–29.9 kg/m^2) or obese (BMI ≥30 kg/m^2; class 1).[7] Lifestyle changes made to promote weight loss may additionally increase physical activity and improve diet, which are important components of secondary prevention in ASCVD in their own right, as previously described.

In the context of increasing rates of severe obesity (BMI ≥40 kg/m^2 or BMI 35–39.9 kg/m^2 with a weight-related comorbidity) and the important but limited efficacy of lifestyle changes on long-term weight loss, other weight-loss interventions may be necessary to produce substantive long-term weight loss for secondary prevention of ASCVD, including bariatric surgery and glucagon-like peptide-1 receptor agonists (GLP-1 RAs).[37–39] Bariatric surgery in patients with established ASCVD has been shown to decrease MACE.[40,41] However, many patients may not be appropriate surgical candidates and/or may prefer not to undergo a surgical procedure. As such, the 2023 AHA/ACC CCD guideline prioritizes lifestyle and pharmacological interventions and recommends referral for bariatric surgery for patients with severe obesity and who have not met weight loss goals with lifestyle and pharmacological measures (class 2a).[7]

GLP-1 RAs function by increasing glucose uptake in peripheral tissues by increasing insulin secretion, slowing gastric emptying, and increasing satiety.[42] Available GLP-1 RA and GLP-1 RA/glucose-dependent insulinotropic polypeptide (GIP) agonists have shown substantive efficacy in weight loss (*Table 2*).[43–49] Cardiovascular outcomes in individuals without diabetes have been evaluated after treatment with semaglutide (GLP-1 RA) in the SELECT trial and with tirzepatide (combined GLP-1 RA/GIP agonist) in the SUMMIT trial.[50,51] In the SELECT trial of semaglutide 2.4 mg weekly in patients with preexisting ASCVD and BMI ≥27 kg/m^2, but no history of diabetes, patients receiving semaglutide treatment had a 20% decrease in a composite endpoint of cardiovascular death, MI, or stroke (HR 0.80; 95% CI [0.72–0.90]).[50] Based on these data and because the STEP8 trial showed improved weight loss with semaglutide compared with liraglutide,[52] the 2023 AHA/ACC CCD guideline supports the selection of semaglutide over liraglutide for weight loss pharmacotherapy.[7] The 2024 SUMMIT trial demonstrated that subcutaneous tirzepatide up to 15 mg weekly in patients with history of heart failure with preserved ejection fraction and BMI ≥30 kg/m^2 decreased rates of a composite outcome of adjudicated death from cardiovascular causes or worsening heart failure event (HR 0.62; 95% CI [0.41–0.95]).[51] Analysis of the components of the composite showed a significant decrease in worsening heart failure events (HR 0.54; 95% CI [0.34–0.85]), but a nonsignificant effect on cardiovascular death (HR 1.58; 95% CI [0.52–4.83]).[51] Overall, treatment with a GLP-1 RA is recommended in patients with ASCVD, BMI ≥30 kg/m^2, or BMI 25–29.9 kg/m^2 with weight-related comorbidity, and who have not met weight-loss goals after lifestyle interventions (class 2a, 2023 AHA/ACC CCD guideline).[7]

Table 3: Expected Lowering of LDL Cholesterol Levels by Available Medication

Drug	Expected LDL Cholesterol Reduction (Mean %)
HMG-CoA Reductase Inhibitors[66]	
Low-intensity statin	<30%
Moderate-intensity statin	30–49%
High-intensity statin	≥50%
PCSK9 Inhibitors	
Alirocumab[67,68]	50–60%
Evolocumab[69–71]	50–60%
ATP Citrate Lyase Inhibitor	
Bempedoic acid[72–76]	17–28%
Cholesterol Absorption Inhibitor	
Ezetimibe[77]	15–20%

HMG = hydroxymethylglutaryl; PCSK9 = proprotein convertase subtilisin/kexin type 9.

Diabetes Management: Sodium-glucose Cotransporter 2 Inhibitors and Glucagon-like Peptide-1 Receptor Agonists

Intensive multifactorial interventions to optimize glucose regulation as well as the treatment of dyslipidemia and hypertension, and ASCVD risk reduction has been shown to decrease risks of cardiovascular death, cardiovascular events, and diabetic complications, such as nephropathy, retinopathy, and autonomic neuropathy.[53,54] Sodium–glucose cotransporter 2 inhibitors (SGLT2i) and GLP-1 RA have emerged as promising treatments for type 2 diabetes (T2D) that additionally improve cardiovascular outcomes. The 2023 AHA/ACC CCD guideline recommends use of either agent (class 1).[7] Studies of SGLT2i, such as empagliflozin, canagliflozin, and dapagliflozin, have all demonstrated improved cardiovascular outcomes.[55–58] Treatment with canagliflozin was notably associated with increased rate of amputation, and SGLT2is as a class have been noted to carry an increased risk for genital infections and euglycemic diabetic ketoacidosis.[55–57] The use of SGLT2is may be limited by estimated glomerular filtration rate (eGFR), and appropriate eGFR cutoffs for therapy depend on indication (eGFR ≥20 ml/min/1.72 m^2 for heart failure,[59–61] eGFR ≥30 ml/min/1.72 m^2 for T2D).[55,56] SGLT2i have also been shown to improve renal outcomes in chronic kidney disease, regardless of T2D status.[62,63]

Trials of GLP-1 RA in patients with T2D additionally show improvement in cardiovascular outcomes, with the SUSTAIN-6 trial investigating semaglutide treatment demonstrating a 26% reduction in the composite outcome of cardiovascular death, MI, and stroke (HR 0.74; 95% CI [0.58–0.95]).[64,65] As described above, treatment with tirzepatide decreased rates of worsening heart failure events in the SUMMIT trial.[51] The SURPASS-CVOT trial (NCT04255433) is currently under way to study cardiovascular outcomes of tirzepatide treatment compared with dulaglutide in patients with T2D.

LDL Cholesterol Management

There are multiple pharmacological options available for the reduction of LDL cholesterol (*Table 3*).[66–77] Statins remain a key pillar of ASCVD

secondary prevention, specifically the use of highest intensity statin therapy tolerated to achieve at least a 50% reduction in LDL cholesterol.[7] The 2023 AHA/ACC CCD guideline recommends to treat to at least a 50% reduction in LDL cholesterol (class 1) and to consider treatment to LDL cholesterol levels <1.81 mmol/l in those at very high risk of ASCVD (those with a history of multiple ASCVD events or previous ASCVD event and multiple predisposing conditions).[7] The 2021 ESC ASCVD prevention guideline recommends LDL cholesterol <1.42 mmol/l for those with established ASCVD.[8] More intensive statin regimens for greater LDL cholesterol reduction have been shown to improve outcomes, with reductions in risk of death due to coronary heart disease by 20% per 1.0 mmol/l LDL cholesterol reduction (rate ratio 0.80; 95% CI [0.74–0.87]).[78] However, substantive residual ASCVD risk may still persist despite statin treatment. An analysis of statin-treated patients with ASCVD in the AIM-HIGH trial cohort found a mean predicted 5-year risk of recurrent ASCVD events of 21.1% (range 7.7–79.7%) with increased risk associated with increased HbA1c (HR 1.10; 95% CI [1.01–1.19]) and lipoprotein(a) (HR 1.07; 95% CI [1.04–1.10]).[79]

Treatment with ezetimibe, which prevents intestinal cholesterol absorption, and treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which prevent degradation of LDL cholesterol receptors in the liver, are two avenues for further risk reduction associated with lipid management. The 2023 AHA/ACC CCD guideline recommends the use of ezetimibe in very high-risk ASCVD patients on maximally tolerated statin therapy and with LDL cholesterol ≥1.81 mmol/l (class 2a).[7] The use of ezetimibe in lower-risk patients on statin therapy and with LDL cholesterol ≥1.81 mmol/l is a class 2b recommendation.[7] The IMPROVE-IT trial comparing ezetimibe and statin combined treatment to moderate-intensity statin monotherapy in adults with recent hospitalization for acute coronary syndrome showed decreased risk of a composite outcome of cardiovascular death, MI, unstable angina, coronary revascularization, or stroke (HR 0.94; 95% CI [0.89–0.99]).[80,81]

The 2022 ACC Expert Consensus on non-statin lipid-lowering therapies recommends the use of PCSK9 inhibitors in very high-risk ASCVD patients and suggests that prioritization of PSCK9 inhibitors over other non-statin therapies is reasonable in these patients who require >25% additional LDL cholesterol lowering.[82] The use of PCSK9 inhibitors in very high-risk ASCVD patients, already receiving statin and ezetimibe, with LDL cholesterol ≥1.81 mmol/l is a class 2a recommendation by the 2023 AHA/ACC CCD guideline in patients with CCD, primarily based on the FOURIER and ODYSSEY OUTCOMES trials.[7,67,69] Based on meta-analysis of these and additional trials, PCSK9 inhibitor treatment reduces risk of a composite outcome of MI, stroke, and cardiovascular death by 20% (relative risk 0.80; 95% CI [0.73–0.87]).[83]

The prioritization of ezetimibe over PCSK9 inhibitors is partly associated with the financial burden of this therapy.[84] The 2023 AHA/ACC CCD guideline classifies addition of ezetimibe in appropriate patients as a high-value intervention, while the addition of PCSK9 inhibitors is of uncertain value.[7] The first Food and Drug Administration-approved PCSK9 inhibitors (evolocumab and alirocumab) are monoclonal antibodies.[85] Inclisiran, a small-interfering RNA that targets PCSK9 messenger RNA was approved in 2021.[85–87] The ORION-10 trial investigating inclisiran treatment in statin-treated patients with ASCVD and the ORION-11 trial in patients either with ASCVD or an ASCVD risk equivalent showed that inclisiran reduced LDL cholesterol by 52.3% (95% CI [48.8–55.7]) and 49.9% (95% CI [46.6–53.1]) respectively.[87] ORION-4 is an ongoing RCT designed to evaluate the impact of inclisiran treatment on risk of cardiovascular events in patients with established ASCVD (NCT03705234).[86]

Bempedoic acid inhibits ATP citrate lyase, an enzyme upstream of hydroxymethylglutaryl CoA-reductase in the cholesterol synthesis pathway in the liver.[76] In the CLEAR-OUTCOMES trial (bempedoic acid in statin-intolerant patients with or at high risk for ASCVD), treatment with bempedoic acid reduced LDL cholesterol and the incidence of MACE (HR 0.87; 95% CI [0.79–0.96]).[76] The 2023 AHA/ACC CCD guideline recommends use of bempedoic acid in patients on maximally tolerated statin therapy with LDL cholesterol ≥1.81 mmol/l and intolerant of ezetimibe and/or PCSK9 inhibitors (class 2b).[7] There are several other LDL cholesterol-lowering agents in development, including cholesteryl ester transfer protein inhibitors (e.g. obicetrapib),[88] oral PCSK9 inhibitors,[85] and lerodalcibep, an anti-PCSK9 small binding protein.[89]

Lipoprotein(a)

As highlighted by an AHA statement, lipoprotein(a) is associated with increased lifetime ASCVD risk.[90] In a cohort of 10,181 individuals with ASCVD, lipoprotein(a) measurements above the 50th percentile were associated with increased incidence of MACE (adjusted HR 1.14 for lipoprotein(a) in the 51–70 percentile; 95% CI [1.05–1.24], adjusted HR 1.21 for lipoprotein(a) in the 71–90 percentile; 95% CI [1.11–1.32], adjusted HR 1.26 for lipoprotein(a) in the 91–100 percentile; 95% [1.12–1.41]).[91] In an analysis of one large primary prevention cohort and two secondary prevention cohorts, elevated levels of lipoprotein(a) were associated with increased risks of MACE regardless of baseline levels of inflammation as determined by high-sensitivity C-reactive protein (hs-CRP).[92]

There are currently no commercially available therapies that specifically target lipoprotein(a) and no direct evidence that targeting lipoprotein(a) decreases cardiovascular events. However, novel lipoprotein(a)-lowering therapies being investigated include pelacarsen (NCT04023552), lepodisiran (NCT06292013), zerlasiran, muvalaplin, and olpasiran (NCT05581303).[86,93,94,95] While pharmacological strategies directly targeting lipoprotein(a) are in development, the association between elevated lipoprotein(a) and increased ASCVD risk supports more aggressive risk factor management and lipid-lowering in patients with elevated lipoprotein(a) (typically defined as lipoprotein(a) >50 mg/dl [125 nmol/l]).[90,95,96] Of note, subgroup analyses of the FOURIER and ODYSSEY OUTCOMES trials found that treatment with PCSK9 inhibitors significantly decreased lipoprotein(a) levels.[97,98]

Hypertriglyceridemia

Having persistent elevated triglycerides (>1.69 mmol/l) has been associated with adverse outcomes for patients with ASCVD in multiple studies, including increased all-cause mortality, MI, non-fatal stroke, and need for coronary revascularization, even when controlling for LDL cholesterol and statin therapy.[99–101] Trials investigating agents such as fibrates and niacin to lower triglycerides have shown minimal to no benefit, and the 2023 AHA/ACC CCD guideline labels use of fibrates or niacin as a class 3: no benefit recommendation.[7,102] As has been reviewed elsewhere, limitations in trial design and the limitations of total triglyceride concentration as a marker for the triglyceride-rich lipoproteins that are more significantly associated with increased ASCVD risk may account, at least in part, for the lack of benefit seen in these studies.[103] Agents directly targeting triglyceride-rich lipoproteins are currently being investigated.[103]

Icosapent ethyl is an ethyl ester of eicosapentaenoic acid (EPA), which has been shown to improve inflammation and endothelial function in physiologic studies.[104] The 2023 AHA/ACC CCD guideline classifies use of icosapent ethyl in patients on maximally-tolerated statin therapy with LDL

cholesterol <2.59 mmol/l and persistent fasting triglycerides 1.69–5.63 mmol/l after lifestyle modification as a class 2b recommendation.[7] Of note, the American Diabetes Association endorses the use of icosapent ethyl in statin-treated individuals with diabetes and established ASCVD with persistently elevated triglycerides as a level A recommendation.[105]

These recommendations are based on the smaller open-label study, JELIS, and the larger RCT, REDUCE-IT.[106,107] The REDUCE-IT trial demonstrated reduced risk of MACE with icosapent ethyl treatment in statin-treated patients with hypertriglyceridemia and with established ASCVD or diabetes and risk factors (HR 0.75; 95% CI [0.68–0.83]).[107] Other formulations of omega-3-fatty acids have not shown to be effective in RCTs.[102,107] For example, the STRENGTH trial investigating treatment of statin-treated patients with hypertriglyceridemia and at high cardiovascular risk with a carboxylic acid formulation of EPA and docosahexaenoic acid showed no benefit in reduction of MACE.[108]

The 2023 AHA/ACC CCD guideline raises concern over the use of mineral oil as placebo in REDUCE-IT due to the adverse effects of mineral oil noted on lipids and other biomarkers, including lipoprotein(a) and hs-CRP, in a sub-study of the REDUCE-IT trial.[7,109] However, a meta-analysis of the impact of mineral oil showed inconsistent and overall nonsignificant effects on lipids and other biomarkers.[110] Several over-the-counter supplements are additionally marketed for use in lipid management, but RCT data demonstrate no significant difference in triglycerides or LDL cholesterol associated with these supplements compared with placebo.[111]

Use of β-blockers

β-blockers, along with RAAS inhibitors, have traditionally been considered first-line therapy for the pharmacological management of hypertension in patients with ASCVD for those with indications such as recent MI or angina (class 1 recommendation, 2023 AHA/ACC CCD guideline).[7] Achieving a blood pressure target of <130/<80 mmHg has been associated with improved cardiac outcomes and lower rates of additional ASCVD events.[7,112] β-blockers, specifically carvedilol, metoprolol succinate, and bisoprolol, are also strongly indicated in ASCVD patients with concomitant heart failure with reduced ejection fraction (left ventricular ejection fraction [LVEF] <50%; class 1 recommendation, 2023 AHA/ACC CCD guideline).[7,113]

Historically, β-blockers were considered standard of care for all patients after MI in perpetuity, regardless of left ventricular systolic function, because of their benefit in decreased myocardial oxygen demand and reduced left ventricular remodeling.[114,115] This recommendation was primarily based on older data from the 1990s and early 2000s showing improved cardiac outcomes, with one 1999 meta-analysis demonstrating long-term treatment with β-blockers after MI decreased risk of death by 23% (95% CI [15–31]).[114–116] More recent data have called into question the long-term use of β-blockers after MI (>1 year). For example, in the REACH registry, use of β-blockers was only associated with decreased risk of composite outcome of cardiovascular death, MI, stroke, and ASCVD-associated hospitalization when limited to patients with history of MI within 1 year (OR 0.77; 95% CI [0.64–0.92]), but was not associated with a significant difference in event rates for the overall cohort of patients with a history of MI.[117] A large Danish cohort study noted that β-blocker treatment 3 months to 3 years after admission for MI had no significant effect on cardiovascular death or recurrent MI.[118] Based primarily on this observational data, the 2023 AHA/ACC CCD guideline recommends re-assessing the need for β-blocker use in patients with ASCVD and history of MI >1 year and without other primary indication for β-blocker use, such as decreased ejection fraction, uncontrolled hypertension, or arrhythmia.[7] Notably, the REDUCE-AMI trial further calls into question the use of β-blockers for secondary prevention in patients post-MI who have LVEF ≥50% and underwent revascularization.[119,120] β-blocker use in this population did not significantly affect outcomes of overall mortality, recurrent MI, cardiovascular death, or heart failure hospitalization.[120] This trial further suggests that the earlier trials that showed more universal benefit of β-blockers after MI may be less applicable now given increased access to improved revascularization procedures; however more data from additional RCTs, of which there are several ongoing, are needed to clarify the issue.[119,120]

Use of Renin–Angiotensin–Aldosterone Inhibitors

Inhibition of the RAAS with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker is strongly indicated for patients with ASCVD and comorbid hypertension, diabetes, LVEF ≤40%, or chronic kidney disease (class 1 recommendation, AHA/ACC).[7] One meta-analysis of five RCTs of ACEi treatment in patients with heart failure or left ventricular dysfunction demonstrated decreased risks of death (OR 0.80; 95% CI [0.74–0.87]) and heart failure hospitalization (OR 0.67; 95% CI [0.61–0.74]).[121] The SAVE and TRACE trials both studied ACEi in patients with left ventricular dysfunction after MI and reported decreased risks of all-cause mortality, cardiovascular mortality, and heart failure progression.[122,123]

In patients with ASCVD and without the comorbid conditions outlined earlier, the benefits of RAAS inhibition are less clear, and the 2023 AHA/ACC CCD guideline classifies their use to decrease cardiovascular events as a class 2b recommendation.[7] Multiple trials have studied RAAS inhibition in these patients, with mixed results. The EUROPA and HOPE trials, investigating perindopril and ramipril respectively, both showed an approximately 20% decrease in the risk of in cardiovascular events.[124,125] However, the QUIET and PEACE studies on quinapril and trandolapril respectively found no significant effect on cardiovascular event rates with treatment.[126,127] These inconsistencies in outcome across trials may also be associated with different rates of other secondary prevention interventions across the various trial populations.[112]

Targeting Systemic Inflammation

Systemic inflammation is increasingly recognized as a key element of ASCVD, especially as data accumulate to support residual inflammatory risk despite statin treatment.[7,128,129] hs-CRP is an inflammatory marker that may identify patients with significant residual ASCVD risk. For example, analysis of the FOURIER trial demonstrated a significant trend in the control group between increased hs-CRP and event rates (cardiovascular death, MI, stroke, all-cause mortality, and coronary revascularization [p for trend <0.0001]).[130] With adjustment for LDL cholesterol achieved during the trial and other confounders, higher baseline hs-CRP was significantly associated with increased rates of the primary composite endpoint (HR 1.09; 95% CI [1.07–1.12] for each doubling in hs-CRP).[130] The JUPITER trial investigated the use of rosuvastatin for primary prevention in individuals with LDL cholesterol <3.36 mmol/l and hs-CRP ≥2.0 mg/l and demonstrated significant reductions in a composite end point of MI, stroke, arterial revascularization, unstable angina hospitalization, or cardiovascular death (HR 0.56; 95% CI [0.46–0.69]), suggesting a benefit of lowering hs-CRP on MACE.[131]

Several studies thereafter have investigated various anti-inflammatory agents for secondary prevention in ASCVD. The CANTOS trial showed that treatment with canakinumab, a monoclonal antibody targeting interleukin-

1β, in patients with previous MI and hsCRP ≥2 mg/l reduced cardiovascular events, supporting the utility of pharmacologically targeting inflammation as a method of secondary prevention.[132] However, widespread recommendations for use of antibody-based interleukin-1β therapy are limited due to cost ineffectiveness.[133] In contrast, the CIRT trial investigating low-dose methotrexate for secondary prevention of ASCVD did not significantly decrease interleukin-1β, interleukin-6, or C-reactive protein and did not affect rates of cardiovascular events when compared with placebo.[134] Ziltivekimab, a monoclonal antibody targeting interleukin-6, has been shown to significantly reduce hs-CRP and other inflammatory markers such as fibrinogen and serum amyloid A in patients with moderate to severe chronic kidney disease and baseline hs-CRP ≥2 mg/l and is currently being further investigated for secondary prevention of ASCVD in this population (ZEUS trial, NCT05021835).[135,136]

Colchicine is a microtubule inhibitor that also targets the interleukin-1β pathway and inhibits neutrophil function.[128,137] Trials investigating colchicine use have shown mixed results, especially when considering their use after acute MI.[137–140] The LoDoCo and LoDoCo2 trials both investigated the effect of colchicine 0.5 mg daily on cardiovascular outcomes in patients with ASCVD and found decreased event rates with colchicine treatment.[137,138] The LoDoCo2 trial found that colchicine treatment conferred a 41% decrease in the composite endpoint of cardiovascular death, MI, stroke, or ischemia-driven coronary revascularization (HR 0.69; 95% CI [0.57–0.83]), although a nonsignificant trend towards increased non-cardiovascular death in the treatment group (HR 1.51; 95% CI [0.99–2.31]) was also noted.[138] The COLCOT trial examined colchicine treatment in patients with recent MI and demonstrated a decreased risk of the composite endpoint of cardiovascular death, cardiac arrest, MI, stroke, or ischemia-driven coronary revascularization (HR 0.77; 95% CI [0.61–0.96]).[139] Based on these data, the 2023 AHA/ACC CCD guideline classifies treatment with colchicine as a class 2b recommendation for patients who remain at very high risk and are already treated with maximally-tolerated conventional guideline-directed medical therapy.[7] In 2024, the CLEAR SYNERGY trial investigated daily colchicine treatment in patients after percutaneous coronary intervention for MI in a larger population than COLCOT and showed no difference in MACE.[140]

Anti-thrombotic Therapies: Rivaroxaban

The benefit of aspirin is well-known in patients with ASCVD, and a substantial portion of patients with ASCVD have indications for additional anti-platelet therapy or for therapeutic oral anti-coagulation.[7] Further research has sought to determine whether additional anti-platelet or anti-coagulation therapies may be appropriate in the broader ASCVD population. The COMPASS trial randomized patients with stable ASCVD to receive rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily, rivaroxaban 5 mg twice daily, or aspirin 100 mg daily.[141] The rivaroxaban plus aspirin group had a decreased incidence of a primary outcome of cardiovascular death, MI, or stroke compared with aspirin alone (HR 0.76; 95% CI [0.66–0.86]).[141] This benefit persisted in subgroup analyses of patients with coronary artery disease, peripheral or carotid artery disease, or diabetes.[142–144] Use of rivaroxaban plus aspirin did increase major bleeding events (HR 1.70; 95% CI [1.40–2.05]) compared with aspirin alone, but rates of intracranial bleeding or fatal bleeding were comparable between the two groups.[141] Thus, the 2023 AHA/ACC CCD guideline recommends the use of rivaroxaban 2.5 mg twice daily and aspirin 81 mg in patients with ASCVD without an indication for therapeutic anti-coagulation or dual anti-platelet therapy, who are high risk for additional ASCVD events and low-moderate bleeding risk (class 2a).[7] The 2021 ESC ASCVD prevention guideline also recommends low-dose rivaroxaban treatment in these individuals (class 2a).[8]

Vaccinations

Evidence supports an association between influenza infection and subsequent acute coronary syndrome.[145,146] In one meta-analysis, patients with acute MI were twice as likely to have had a recent influenza or other respiratory tract infection (pooled OR 2.01; 95% CI [1.47–2.76]).[147] This link appears to be mediated by increased inflammation as well as direct effects of the virus on atherosclerotic plaques.[146] Correspondingly, influenza vaccination has been shown to be effective for secondary prevention in patients with ASCVD.[148–150] The IAMI trial, an RCT of influenza vaccine administration to patients with recent MI, showed that influenza vaccination decreased the risks of all-cause death (HR 0.59; 95% CI [0.39–0.89]), cardiovascular death (HR 0.59; 95% CI [0.39–0.90]), and MI (HR 0.86; 95% CI [0.50–1.46]) when compared with placebo.[151] Annual influenza vaccination in patients with ASCVD is a class 1 recommendation by the 2023 AHA/ACC CCD guideline.[7]

There are fewer data available for pneumococcal vaccination for secondary prevention in patients with ASCVD, although the 2023 AHA/ACC CCD guideline recommends it (class 2a), based on the data available.[7]

Further data are necessary on the long-term impact of vaccination for COVID-19 on cardiovascular event rate. However, full and partial vaccination substantively decreases the rate of MACE associated with COVID-19 (full completion of the vaccination schedule: HR 0.59; 95% CI [0.55–0.63]; partial completion of the vaccination schedule: HR 0.76; 95% CI [0.65–0.89]), and thus is recommended by the 2023 AHA/ACC CCD guideline (class 1).[7,152]

Conclusion

There is a multitude of targets that have shown benefit for the secondary prevention of ASCVD. It is additionally key to note that social determinants of health play a substantive role regarding outcomes in ASCVD and may affect management of any of the previously described targets.[153] Ample data support these interventions to decrease residual risk in patients with established ASCVD, and these interventions should be strongly considered dependent on individual patient characteristics. ❑

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