Pharmacologic Prevention of Atherosclerotic Cardiovascular Events

By Jonathan D. Cicci, Pharm.D., BCPS, BCCP, CPP; and Prashanth Iyer, Pharm.D., BCPS

Reviewed by Tracy E. Macaulay, Pharm.D., FCCP, FACC, BCPS-AQ Cardiology, BCCP; and Christie Schumacher, Pharm.D., FCCP, BCPS, BCACP, BCCP, BC-ADM, CDCES

LEARNING OBJECTIVES

1. Develop an optimal lipid-lowering regimen for a given patient with or without established atherosclerotic cardiovascular disease (ASCVD) disease.
2. Design an optimal medication regimen for a patient with established ASCVD and elevated triglycerides using recent literature on omega-3 fatty acids.
3. Evaluate patient-specific risk factors for ASCVD and distinguish between patients who may or likely will not benefit from aspirin therapy.

ABBREVIATIONS IN THIS CHAPTER

ACC	American College of Cardiology
AHA	American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
CHD	Coronary heart disease
CV	Cardiovascular
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
DM	Diabetes mellitus
EPA	Eicosapentaenoic acid
ESC	European Society of Cardiology
MI	Myocardial infarction
O3FA	Omega-3 Fatty acid

Table of other common abbreviations

INTRODUCTION

Cardiovascular disease is the leading cause of death in the United States and has a higher annual mortality rate than all forms of cancer and chronic lower respiratory diseases combined (Benjamin 2019). Coronary artery disease and stroke account for more than 60% of CV deaths in the United States, making the primary and secondary prevention of ASCVD a significant public health concern (Benjamin 2019). Several therapies are commonly used for ASCVD prevention and treatment, including statins, O3FA, and aspirin. This chapter summarizes current professional guidelines and recent clinical trials for each therapy in the primary and secondary prevention of ASCVD and highlights the key differences among them with important landmark trials.

STATINS IN PRIMARY AND SECONDARY PREVENTION

Statins in Primary Prevention

Recent Literature

The benefits of statins for primary prevention of ASCVD were first described in the early to mid 1990s. However, the number of trials of statins for primary prevention pales in comparison to those for secondary prevention. Although a complete review of the historical data is beyond the scope of this chapter, several key points are worth summarizing.

The Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial randomized 12,705 patients without CVD to rosuvastatin 10 mg/day or placebo (Yusuf 2016). Patients were age 55 years or older (men) or 60 years or older (women) and at intermediate CV risk with 1 or more risk factors at enrollment. At median follow-up of 5.6 years,

the rosuvastatin group had lower rates of the co-primary end points of CV death, nonfatal MI, or nonfatal stroke (HR 0.76; 95% CI, 0.64–0.91; p=0.002) and of CV death, nonfatal MI, nonfatal stroke, revascularization, heart failure, or cardiac arrest (HR 0.75; 95% CI, 0.64–0.88; p<0.001). Benefit was primarily driven by reductions in MI (35%), stroke (30%), and revascularization (32%); however, rates of CV death and all-cause mortality were similar between groups. The HOPE-3 trial provided important insight into statins for primary prevention in a modern population.

Subsequently, the U.S. Preventive Services Task Force conducted an updated systematic review and meta-analysis of 19 trials (71,344 patients) assessing statin versus placebo or no statin in patients without CVD (Chou 2016). Although statin therapy was associated with reductions in all-cause mortality (RR 0.86; 95% CI, 0.80–0.93; I^2=0%) and CV death (RR 0.82; 95% CI, 0.71–0.94; I^2=0%), few trials independently found reductions in all-cause CV death (1 trial) or mortality (2 trials). Statins were also associated with reductions in MI (RR 0.64; 95% CI, 0.57–0.71; I^2=0%), stroke (RR 0.71; 95% CI, 0.62–0.82; I^2=0%), and composite CV outcomes (RR 0.70; 95% CI, 0.63–0.78; I^2=36%). The authors noted that absolute benefit increased as baseline CV risk increased, a relationship that has been often noted in the literature on statin use in primary prevention (Chou 2016).

Primary Prevention Guidelines

The 2019 ACC/AHA primary prevention guidelines consider two main categories of patients: those with comorbid conditions necessitating statin therapy, and those without comorbid conditions who require a risk assessment and possibly a risk discussion, as shown in Table 1 and Table 2 (Arnett 2019).

The first group in the 2019 ACC/AHA primary prevention guidelines includes patients with DM or those with LDL 190 mg/dL or more (Arnett 2019). Good evidence from randomized controlled clinical trials supports the use of moderate-intensity statins for primary prevention in patients with DM between ages 40–75 years regardless of calculated ASCVD risk score. Although high-intensity statins have not been specifically studied in this patient population for primary prevention, patients with DM are at a higher risk for ASCVD events. As such, it may be reasonable to use high-intensity statins in these patients. The decision to use a high-intensity statin in patients with DM for primary prevention hinges on two key factors: assessment of DM-specific risk modifiers and ASCVD risk factors and engaging in a patient-specific risk discussion. It is reasonable to favor high-intensity statins as patients develop DM-specific risk modifiers (Box 1) or for those with several ASCVD risk factors (Box 2) (Arnett 2019). Of note, the 2018 ACC/AHA cholesterol guidelines also stated that it may be reasonable to add ezetimibe to maximally tolerated statin therapy in patients with DM and ASCVD score 20% or more to reduce LDL by at least 50% (Grundy 2018). However, this recommendation is not included in the 2019 ACC/AHA primary prevention guidelines.

In contrast, patients with LDL 190 mg/dL or more between ages 20–75 years are rarely included in large randomized controlled trials, although these patients have a high lifetime risk for ASCVD events. High-intensity statins are preferred in this group because the treatment goal is to reduce LDL by at least 50%, and moderate- or low-intensity statins are unlikely to achieve sufficient LDL reduction. Although not specifically addressed in the 2019 ACC/AHA primary prevention guidelines, it is not uncommon for these patients to require adjunctive therapies such as ezetimibe or proprotein convertase

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology leading to atherosclerotic cardiovascular disease
- Understanding of primary and secondary prevention definitions
- Lipid goals defined by the leading professional cardiovascular societies
- Statin intensity
- Pooled cohort equation risk assessment tool
- Various lipid-lowering and antiplatelet medications used to treat and prevent atherosclerotic cardiovascular disease
- Consequences of poorly managed atherosclerotic cardiovascular disease

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American College of Cardiology. ASCVD Risk Estimator Plus.
- 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e285-350.
- 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:e177-232
- Anderson JL, Morrow DLA. Acute myocardial infarction. N Engl J Med 2017;376:2053–64

Table 1. Summary of the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease Recommendations for Statins Based on Age and Comorbidities

Patient Group	Recommendation	Grade
LDL ≥190 mg/dL; age 20–75 yr	No risk assessment; initiate high-intensity statin	COR I, LOE B-R
Diabetes and age 40–75 yr	Initiate moderate-intensity statin	COR I, LOE A
	Risk assessment to consider high-intensity statin	COR IIa, LOE B-R
Age >75 yr	Clinical assessment and risk discussion	Not graded
Age 20–39 yr	Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk Consider statin if family history of premature ASCVD and LDL ≥ 160 mg/dL[a]	
Age 0–19 yr	Lifestyle to prevent or reduce ASCVD risk	

[a]Family history is defined in Box 2.

ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; COR = class of recommendation; LDL = low-density lipoprotein cholesterol; LOE = level of evidence.

Information from: Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:e177-232.

subtilisin/kexin type 9 inhibitors. These adjunctive therapies have not been studied in other patients for primary prevention and are not specifically recommended by the 2019 ACC/AHA primary prevention guidelines (Arnett 2019).

The 2019 ACC/AHA primary prevention guidelines recommend a risk assessment and/or a risk discussion for all other patients who do not have established ASCVD, DM, or LDL 190 mg/dL or more. The risk assessment should be conducted using the pooled cohort equation; the results of the risk assessment will determine whether a risk discussion is recommended. The guidelines separate patients into one of four categories based on calculated risk (see Table 2). The risk discussion for patients at the extremes (low risk and high risk) tends to be more straightforward. Low-risk patients (risk

Table 2. Summary of the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease Recommendations for Statins Based on Calculated Risk Level

Risk Score for Adults age 40–75 yr with LDL ≥70 to <190 mg/dL and without diabetes	Recommendation	Grade
<5% (low risk)	Emphasize lifestyle to reduce risk factors	COR I
5% to <7.5% (borderline risk)	Presence of risk-enhancing factors may justify initiation of moderate-intensity statin	COR IIb, LOE B-R
≥7.5% to <20% (intermediate risk)	A moderate-intensity statin should be recommended after a patient-centered risk discussion	COR I, LOE A
	LDL should be reduced by ≥30% or reduced by ≥50% for optimal ASCVD risk reduction	COR I, LOE A
	Risk-enhancing factors favor initiation or intensification of statin[a]	COR IIa, LOE B-R
≥20% (high risk)	Initiate statin to reduce LDL ≥50%	COR I

[a]Risk-enhancing factors are listed in Box 2.

ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; COR = class of recommendation; LDL = low-density lipoprotein cholesterol; LOE = level of evidence.

Information from: Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:e177-232.

Box 1. Diabetes-Specific Risk Enhancers in Patients with Diabetes According to the 2019 ACA/AHA Primary Prevention Guidelines

- Albuminuria ≥30 mcg albumin/mg creatinine
- Ankle brachial index <0.9
- Estimated glomerular filtration rate <60 mL/min/1.73 m^2
- Long duration of diabetes: ≥10 years for type 2 or ≥20 years for type 1
- Neuropathy
- Retinopathy

ACA = American College of Cardiology; AHA = American Heart Association.

Information from: Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:e177-232.

less than 5%) typically do not require pharmacologic therapy; however, a healthy lifestyle should be emphasized to minimize long-term risk. Conversely, high-risk patients (risk 20% or more) would likely benefit from high-intensity statin therapy with a goal of reducing LDL by at least 50%. Adjunctive therapies such as ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors have not been studied for primary prevention of ASCVD in these populations. Recommendations for the high-risk group are largely extrapolated from meta-analyses and the observation that for primary prevention the patients with the highest baseline risk receive the largest benefit from statins (Chou 2016).

In addition to calculating a risk score, the borderline- and intermediate-risk groups require assessment of risk-enhancing factors to determine appropriate therapy (see Box 2). It is important to note that these risk-enhancing factors for ASCVD are distinct from the DM-specific risk-enhancing factors (see Box 1) (Arnett 2019).

After a patient-centered risk discussion, intermediate-risk patients (risk 7.5% to less than 20%) will likely benefit from the addition of at least a moderate-intensity statin, as evidenced by the HOPE-3 trial. For intermediate-risk patients who also have risk-enhancing factors, increasing to a high-intensity statin provides optimal ASCVD risk reduction. Assessing risk-enhancing factors in this group is critical because it determines statin intensity. Of note, if the risk decision is still uncertain, measurement of a coronary artery calcium (CAC) score may be considered. A score of zero indicates low risk; statin therapy may be omitted at that time unless the patient has DM, a family history of premature coronary artery disease, or is a current smoker. A CAC score 1–99 favors statin therapy, especially if the patient is older than 55 years. A CAC score 100 or more and/or in the 75th percentile or higher also favors initiation of statin therapy, regardless of age (Arnett 2019).

Box 2. 2019 ACC/AHA Primary Prevention Guideline Risk-Enhancing Factors for Patient-Centered Risk Discussions

- Family history of premature ASCVD: men age <55 yr; women age <65 yr
- LDL 160–189 mg/dL or non-HDL 190–219 mg/dL
- Metabolic syndrome[a]
- Chronic kidney disease: estimated glomerular filtration rate 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplant
- Chronic inflammatory conditions, such as psoriasis, lupus, rheumatoid arthritis, HIV/AIDS
- Premature menopause, before age 40 yr
- History of pregnancy-associated conditions that increase future ASCVD risk, such as preeclampsia
- High-risk race or ethnicity, such as South Asian ancestry
- Lipids or biomarkers associated with increased ASCVD risk:
  - Persistently elevated primary hypertriglyceridemia (≥175 mg/dL, nonfasting)
  - If measured:
    - Elevated high-sensitivity C-reactive protein (≥2.0 mg/dL)
    - Elevated lipoprotein(a) ≥50 mg/dL or ≥125 mg/dL[b]
    - Elevated apolipoprotein B ≥130 mg/dL[c]
    - Ankle brachial index <0.9

[a]Requires ≥3 of the following: increased waist circumference (≥40 inches in men; ≥35 inches in women), triglycerides >150 mg/dL (nonfasting), elevated blood pressure, elevated glucose, HDL <40 mg/dL (men) or <50 mg/dL (women).

[b]A relative indication for measuring lipoprotein(a) is family history of premature ASCVD.

[c]A relative indication for measuring apolipoprotein B is triglycerides ≥200 mg/dL.

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

Information from: Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:e177-232.

Of the four risk categories, the borderline-risk group (5% to less than 7.5%) represents the population with the least amount of data to guide optimal statin therapy. Borderline-risk patients may or may not benefit from statins, and the guidelines suggest moderate-intensity statin therapy only in the presence of risk-enhancing factors. This group would benefit from additional trials to further delineate the role of statin therapy (Arnett 2019).

Future Directions

The Statin Therapy for Reducing Events in the Elderly (STAREE) trial is a prospective, randomized, placebo-controlled, blinded study assessing atorvastatin 40 mg/day versus placebo in 18,000 healthy adults patients age 70 years or older (ClinicalTrials.gov identifier: NCT02099123). This trial will help to clarify the potential risks and benefits of statins for primary prevention in the older adults, a patient population

that has often been underrepresented in previous clinical trials. Other key gaps in the literature include elucidating the effect of statins for primary prevention in patients age 20–39 years, clarifying the accuracy of the pooled cohort equation calculator, and determining optimal frequency of screening for ASCVD risk in patients without ASCVD.

Statins in Secondary Prevention

Historic Benefit of Statins in Secondary Prevention

The role of statins in secondary prevention of ASCVD was first documented in 1994 by the Scandinavian Simvastatin Survival Study (4S) Group (Randomised trial [no author] 1994). Investigators randomized 4444 patients with a history of CHD and hyperlipidemia to simvastatin 20 mg/day or placebo. The simvastatin dose was titrated to achieve a serum TC of 3.0–5.2 mmol/L (116–200 mg/dL). The average patient was a 60-year-old man with a history of MI, a baseline TC of 260 mg/dL, HDL of 46 mg/dL, and LDL of 188 mg/dL. At median follow-up of 5.4 years, 12% of patients in the placebo group had died compared with 8% in the simvastatin group (RR 0.70; 95% CI, 0.58–0.85). Most deaths in both groups were related to CHD (RR 0.58; 95% CI, 0.46–0.73). The reduction in death caused by CHD was consistent in subgroup analyses based on sex and age older than 60 years. Although the 4S trial only included patients with a TC greater than 212 mg/dL, another study included 9014 patients with a TC between 155–217 mg/dL and a history of CHD (Long-Term Intervention with Pravastatin in Ischaemic Disease [LIPID] Study Group 1998). Patients were randomized to pravastatin 40 mg/day or placebo and followed for a median of 6.1 years. Similar to the 4S trial, the LIPID trial found significant reductions in all-cause mortality (RR 0.78; 95% CI, 0.69–0.87) and death caused by CHD (RR 0.76; 95% CI, 0.65–0.88).

High-Intensity Statins in Secondary Prevention

Based on the findings of the 4S and LIPID trials, the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) investigators sought to identify the optimal LDL value. The study randomized 4162 patients with a recent acute coronary syndrome to pravastatin 40 mg/day (moderate intensity) or atorvastatin 80 mg/day (high intensity) (Cannon 2004). At enrollment, median concentrations were TC 180 mg/dL, HDL 39 mg/dL, and LDL 106 mg/dL. At a mean follow-up of 24 months, the high-intensity group had a 16% reduction in the incidence of death from any cause or major CV event (HR 0.84; 95% CI, 0.74–0.95). In patients not taking a statin before the study, LDL decreased by 22% in the pravastatin arm and 51% in the atorvastatin arm. At the end of the study, median LDL was 95 mg/dL in the pravastatin arm and 62 mg/dL in the atorvastatin arm.

Guidelines for Statins in Secondary Prevention

Based on the studies just described, the 2013 ACC lipid guidelines recommend the use of high-intensity statins (atorvastatin 40–80 mg/day, rosuvastatin 20–40 mg/day) for secondary prevention in all patients younger than 75 years with clinical ASCVD without contraindications (Stone 2014). The 2013 guidelines recommended moderate-intensity statins for patients older than 75 years or those with concomitant drug–drug interactions or a history of statin intolerance. In 2018, ACC revised the recommendation by categorizing patients according to risk of future ASCVD events.

For patients deemed to be very high risk (Box 3), multisociety guidelines now recommend initiation of a high-intensity statin, regardless of age. For patients not considered to be very high-risk, a high-intensity statin is recommended for all patients younger than 75 years and is a reasonable alternative to moderate-intensity for patients older than 75 years. Specifically, the 2018 guidelines note that if an LDL less than 70 mg/dL and/or non-HDL less than 100 mg/dL cannot be reached, adding nonstatin therapies such as ezetimibe and/or proprotein convertase subtilisin/kexin

Box 3. Very High-Risk Features of Future ASCVD Events[a]

Major ASCVD Events

- History of ischemic stroke
- History of myocardial infarction (other than recent ACS event)
- Recent ACS (within 12 months)
- Symptomatic peripheral arterial disease: history of claudication with ankle brachial index <0.85 or previous revascularization or amputation

High-Risk Conditions

- Age ≥65 yr
- Heterozygous familial hypercholesterolemia
- History of coronary artery bypass grafting or percutaneous coronary intervention unrelated to a major ASCVD event
- Diabetes
- Hypertension
- Chronic kidney disease: estimated glomerular filtration rate 15–59 mL/min/1.73 m^2
- Current smoking
- Persistently elevated low-density lipoprotein cholesterol ≥ 100 mg/dL despite maximally tolerated statin and ezetimibe therapy
- History of congestive heart failure

[a]Patients with a history of several major ASCVD events or 1 major ASCVD event and several high-risk conditions are considered to be very high risk.

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease.

Information from: Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e285–350.

type 9 inhibitors should be considered. Notably, the definition of *very high risk* is subject to debate.

Although the benefit of statins for secondary prevention is unquestioned, the optimal reduction of cholesterol remains uncertain. Over the past decade, ACC guidelines have alternated between LDL targets and LDL percent reduction. The 2018 ACC guidelines settled on an LDL target of less than 70 mg/dL, whereas the 2019 ESC/European Atherosclerosis Society guidelines have suggested an even more aggressive LDL target of less than 55 mg/dL. For more on this controversy, see the chapter on therapeutic targets.

OMEGA-3 FATTY ACIDS

Primary Prevention of ASCVD

Despite advances in ASCVD treatment and lipid-lowering therapies, residual CV risk remains high (Benjamin 2019; Ganda 2018; Toth 2019). About 25% of the U.S. National Health and Nutrition Examination Survey (1999–2014) participants had TG concentrations of 150 mg/dL or more, and the number of patients is expected to increase further as the global rates of obesity, DM, and metabolic syndrome continue escalating (Ganda 2018). Several observational, post-hoc, and/or Mendelian trials have identified TG as a possible modifiable risk factor for reducing ASCVD events (Ganda 2018; Toth 2019; Bhatt 2017; Nicholls 2018; Aung 2018). Unfortunately, several prospective, randomized, controlled clinical trials have failed to demonstrate meaningful improvements in ASCVD outcomes with the addition of TG-lowering therapy added to background statin therapy (ACCORD Study Group 2010; AIM-HIGH Investigators 2011; HPS2-THRIVE Collaborative Group 2014). It is important to note that these trials did not specifically enroll patients with elevated TG levels.

Historic Literature

Observational studies have noted a decrease in CHD events in populations who consume fish one to two times per week, leading to an interest in using O3FA supplements to augment ASCVD risk reduction (Nicholls 2018; Aung 2018). Two main types of O3FA are found in fish: EPA and DHA. In addition to acting as a free radical scavenger, EPA may reduce several inflammatory markers, including C-reactive protein, lipoprotein-associated phospholipase A2, and apolipoprotein C-III. These effects result from the incorporation of EPA into cellular membranes within an atherosclerotic plaque and interference with lipid oxidation and cellular pathways, which causes inflammation, endothelial dysfunction, and plaque instability (Ganda 2018; Bhatt 2017). Conversely, DHA is more closely associated with neurologic tissue and differs structurally and molecularly from EPA. In addition, DHA appears less stable than EPA and is more likely to undergo rapid conformational changes (Ganda 2018). Of note, DHA has been associated with increases in LDL which may blunt any cardioprotective effects, although this effect is debated (Bhatt 2017, Nicholls 2020).

Despite compelling pathophysiologic data from observational and preclinical trials, randomized controlled clinical trials of O3FA have largely been disappointing. In 2018, the Omega-3 Treatment Trialists' Collaboration published a systematic review and meta-analysis assessing O3FA supplement use and CVD risk (Aung 2018). Eligible publications were required to be randomized clinical trials of O3FA supplements compared with placebo or open-label controlled trials, have a sample size of 500 or more patients and include at least 1 year follow-up. Overall, risk of selection bias was low. Doses of EPA ranged from 226–1800 mg/day and DHA ranged from 0–1700 mg/day. The weighted mean follow-up was 4.4 years. Rates of major vascular events were similar between groups (RR 0.87; 95% CI, 0.93–1.01; p=0.10), as were the rates of CHD events (RR 0.96; 95% CI, 0.89–1.01; p=0.12), any stroke (RR 1.03; 95% CI, 0.93–1.13; p=0.60), and any revascularization (RR 0.99; 95% CI, 0.94–1.04; p=0.60). No significant heterogeneity was detected for nonfatal MI, CHD death, any CHD events, or all major vascular events. Some heterogeneity was detected between open-label and blinded trials for participants with CHD (open-label: RR 0.85; 95% CI 0.72–0.99; p=0.1; blinded: RR 0.99; 95% CI, 0.91–1.07; p=0.69; heterogeneity p=0.03). No heterogeneity was detected for fatal CHD or nonfatal MI. No significant association was found between O3FA supplementation and the reduction of major vascular events in both the overall study population and each relevant subgroup over a mean of 4.4 years.

ASCEND and VITAL

Two trials, ASCEND and VITAL, were published soon afterward and included similar designs (Table 3) (ASCEND 2018b; Manson 2019). Both trials included patients without known ASCVD, and patients were randomized to O3FA 1 g/day (EPA 460 mg/day and DHA 380 mg/day) or placebo containing olive oil. At a mean follow-up of 7.4 years in the ASCEND trial, rates of the primary end point of MI, stroke, transient ischemic attack, or vascular death were similar between groups (Table 4). Multiple hypothesis testing of secondary and exploratory end points was allowed without formal p-value adjustment. In these analyses, rates of MI, stroke, and revascularization were similar between groups. Vascular death was numerically lower in the O3FA group (RR 0.81; 95% CI, 0.67–0.99) in an exploratory analysis and should be interpreted with caution. Rates of major bleeding were low in both groups (ASCEND 2018b).

Similarly, the VITAL trial found comparable rates of the primary end point of MI, stroke, or CV death between the O3FA and placebo groups (see Table 4) (Manson 2019). Rates of stroke and CV death were also similar between groups. Total MI was numerically lower in the O3FA group (HR 0.72; 95% CI, 0.59–0.90) in an exploratory analysis and should be interpreted with caution (Manson 2019). Rates of GI bleeding were similar in both groups (HR 0.99; 95% CI, 0.86–1.14; p=0.89),

Table 3. Key Design and Baseline Characteristics of Recent Randomized Controlled Trials Assessing Omega-3 Fatty Acids vs. Placebo

Trial (Year)	ASCEND (2018)[a]	VITAL (2019)	REDUCE-IT (2019)	STRENGTH (2020)
Participants (n)	15,480	25,871	8179	13,078
Comparison	n-3 (omega-3) Fatty acid 1 g/day vs. placebo (olive oil)		Icosapent ethyl 2 g BID vs. placebo (mineral oil)	Omega-3 Carboxylic acid 4 g/day vs. placebo (corn oil)
Inclusion criteria	Age ≥40 yr with diabetes and without CVD	Age ≥50 yr (men) or ≥55 yr (women) without CVD	Age ≥45 yr with CVD OR Age ≥50 yr with DM + ≥1 risk factor	Age ≥18 yr with ASCVD or DM with ≥1 risk factor (≥ 40 yr men or ≥ 50 yr women) OR Primary prevention with ≥1 risk factor (age ≥50 yr men or ≥60 yr women)
Lipid requirements (mg/dL)	None		TG 135–499 (initial) TG 200–499 (amended) LDL 41–100	LDL <100, TG ≥ 180 and <500 HDL <42 (men) or <47 (women)
Key Baseline Characteristics				
Age, yr (mean ± SD)	63.3±9.2	67.1±7.1	64 (77–69) (median, IQR)	62.5±9
Hypertension (%)	61.6	49.8	Not reported	87.3
Diabetes (%)	94.1	13.7	58.5	70.1
Statin use (%)	75.3	34.4	62.5 (moderate-intensity) 30.8 (high-intensity)	50.1 (low/moderate-intensity) 49.9 (high-intensity)
Ezetimibe use (%)	Not reported		6.4	3.7
Median TG (mg/dL)	Not measured		216	240
Risk cohorts	Low (<5%): 40.5% Moderate (5–10%): 42.3% High (≥10%): 17.2%	None specified	Primary prevention 29.3% Secondary prevention 70.7%	Primary prevention 44.1% Secondary prevention 55.9%

[a]ASCEND risk cohort refers to a 5-year risk of a serious vascular event.

ASCVD = atherosclerotic cardiovascular disease; BID = twice daily; CVD = cardiovascular disease; DM = diabetes mellitus; HDL = high-density lipoprotein cholesterol; IQR = interquartile range; LDL = low-density lipoprotein cholesterol; TG = triglyceride.

Information from: ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus. N Engl J Med 2018;379:1540-50; Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11-22; Budoff MJ, Bhatt DL, Kinninger A, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. Eur Heart J 2020;41:3925-32; Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. JAMA 2020;324:2268-80.

as were the rates of hematuria, easy bruising, and frequent nosebleeds.

The ASCEND and VITAL trials appear to confirm the results of the 2018 meta-analysis, which found scant evidence for the use of O3FA for the prevention of major adverse CV events. This point is particularly important given that the trials included more than 41,000 patients with modern therapy and extended follow-up. Based on the preponderance of evidence, 1 g O3FA daily should not be recommended for the primary or secondary prevention of ASCVD.

Secondary Prevention of ASCVD

REDUCE-IT

Conversely, icosapent ethyl is a highly purified (96% or higher) EPA ethyl ester that appears to reduce TG, TG-rich lipoproteins, and factors related to their metabolism. Of importance, icosapent ethyl does not appear to increase LDL levels (Bhatt 2017; Bays 2011). The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) randomized 8179 patients to icosapent ethyl 2 g twice daily or placebo containing mineral oil (see Table 3) (Bhatt 2019). After a median follow-up of 4.9 years, randomization to icosapent ethyl was associated with a 25% reduction in the primary end point of CV death, MI, revascularization, or unstable angina

Table 4. Key Results of Recent Randomized Controlled Trials Assessing Omega-3 Fatty Acids vs. Placebo

Trial (Year)	ASCEND (2018)	VITAL (2019)	REDUCE-IT (2019)	STRENGTH (2020)
Participants (n)	15,480	25,871	8179	13,078
Comparison	n-3 (omega-3) Fatty acid 1 g/day vs. placebo (olive oil)		Icosapent ethyl 2 g BID vs. placebo (mineral oil)	Omega-3 Carboxylic acid 4 g/day vs. placebo (corn oil)
Follow-up (yr, median)	7.4 (mean)	5.3	4.9	3.5
Primary end point[a] HR or RR (95% CI)	RR 0.97 (0.87–1.08); p=0.55	HR 0.92 (0.80–1.06); p=0.24	HR 0.75 (0.68–0.83); p<0.001 NNT 21	HR 0.99 (0.90–1.09); p=0.84
Fatal or nonfatal MI	RR 0.93 (0.76–1.14)[b]	HR 0.72 (0.59–0.90)[c] p=not reported (exploratory)	HR 0.69 (0.55–0.78); p<0.001 NNT 39	HR 0.97 (0.81–1.17)[b] p=0.77
CV death	RR 0.81 (0.67–0.99)[d] p=not reported (post-hoc)	HR 0.96 (0.76–1.21)[c] p=not reported (exploratory)	HR 0.80 (0.66–0.98); p=0.03 NNT 112	HR 1.09 (0.90–1.31); p=0.37

[a]Primary end points: ASCEND: Vascular death (excluding intracranial hemorrhage), MI, stroke, or transient ischemic attack (note: transient ischemic attack was added to the primary end point during enrollment to increase statistical power); presented as rate ratio; VITAL: MI, stroke, or CV death; REDUCE-IT: CV death, MI, revascularization, or unstable angina; STRENGTH: CV death, MI, stroke, revascularization, or unstable angina.

[b]Presented as rate ratio for nonfatal MI only; outcome of fatal or nonfatal MI not reported

[c]No control was used for multiple hypothesis testing, and no formal adjustment was made to the p values or CIs; thus, the results regarding exploratory end points and subgroups should be interpreted with caution.

[d]Presented as RR for vascular death (excluding intracranial hemorrhage); conducted a post-hoc exploratory analysis

BID = twice daily; CI = confidence interval; CV = cardiovascular; MI = myocardial infarction.

Information from: ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus. N Engl J Med 2018;379:1540-50; Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11-22; Budoff MJ, Bhatt DL, Kinninger A, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. Eur Heart J 2020;41:3925-32; Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. JAMA 2020; 324:2268-80.

(see Table 4). Similarly, icosapent ethyl was associated with a significant 20% reduction in CV death, 28% reduction in total MI, 32% reduction in hospitalization for unstable angina, and 28% reduction in total stroke. Results appeared consistent regardless of baseline TG value or statin intensity. Of importance, the benefit appeared more pronounced in the secondary prevention cohort (HR 0.72; 95% CI, 0.63–0.82) compared with the primary prevention cohort (HR 0.81; 95% CI, 0.62–1.06); however, because of wide confidence intervals, this benefit did not achieve conventional significance (interaction, p=0.54) (Bhatt 2019). Rates of bleeding disorders were similar between groups (2.7% vs. 2.1%, p=0.06), but icosapent ethyl was associated with an increase in atrial fibrillation (5.4% vs. 3.9%, p=0.03).

The results of REDUCE-IT stand in stark contrast to those of the ASCEND and VITAL trials, as well as the almost-dozen trials preceding them. Contrary to previous trials, REDUCE-IT enrolled a predominantly secondary prevention population, required baseline elevated TGs, and used high-dose, high-purity EPA (Bhatt 2019). These differences may explain the overwhelmingly positive results of the trial compared with previous efforts. Conversely, patients in REDUCE-IT typically received suboptimal statin doses, and the mineral oil placebo may have interfered with statin absorption and increased pro-atherosclerotic biomarkers. However, the FDA reviewers indicated the 10% increase in LDL in the placebo group accounted for only 3% of excess CV risk, which was insufficient to account for the observed benefit (Hughes 2019). In addition, the FDA noted higher rates of total bleeding (11.8% vs. 9.9%) during review which are substantially higher than those reported in the primary publication (Bhatt 2019; Hughes 2019). Despite these issues, icosapent ethyl received FDA approval to reduce the risk of CV events in patients with TG 150 mg/dL or more and with either established CVD or DM and 2 or more risk factors.

EVAPORATE Trial

Subsequently, the EVAPORATE trial evaluated the effect of icosapent ethyl on plaque volumes seen on coronary computer tomographic angiography in patients taking statin therapy with TG 135–499 mg/dL and LDL 40–115 mg/dL. Participants had known coronary atherosclerosis and were randomized to icosapent ethyl 2 g twice daily or mineral oil placebo. Of the 80 patients (age 30–85 years) enrolled, 64 patients completed the 18-month follow-up. Icosapent ethyl was associated with a 17% reduction in low-attenuation plaque volume compared with a 109% increase in the placebo group. In addition, icosapent ethyl was associated with reductions in volume of other plaque types whereas mineral oil placebo was associated with an increase as follows: fibrofatty (–34% vs. +32%), fibrous (–20% vs. +1%), calcified (–1% vs. +15%), total noncalcified (–19% vs. 9%) and total plaque (–9% vs. 11%) (Budoff 2020). The EVAPORATE trial raised important questions about how the mineral oil placebo may have affected the results of REDUCE-IT.

STRENGTH

The STRENGTH trial randomized 13,078 patients with (55%) or without (45%) ASCVD to 4 g of omega-3 carboxylic acid (CA) (75% EPA, 25% DHA) or corn-oil placebo (see Table 3) (Nicholls 2020). After a median follow-up of 42 months, the trial was terminated because of futility. The rate of the primary end point of CV death, MI, stroke, revascularization or unstable angina was similar between omega-3 CA and placebo (see Table 4). Rates of individual end points of CV death, nonfatal MI, nonfatal stroke, revascularization, and unstable angina were also similar between groups. Results did not differ in the secondary or primary prevention cohorts (interaction, p=0.07). Of importance, rates of new-onset atrial fibrillation were higher in the omega-3 CA group (2.2% vs. 1.3%; HR 1.69; 95% CI, 1.29–2.21; nominal p<0.001). Notably, corn oil

Patient Care Scenario

A 55-year-old man has not had a health evaluation in 30 years. He now has a recent diagnosis of hypertension (blood pressure 155/92 mm Hg) and DM (hemoglobin A1C 9%). He denies drug, alcohol or tobacco use. His BMI is 22 kg/m^2. Current lipid panel results are TC 220 mg/dL, LDL 140 mg/dL, HDL 30 mg/dL, and TG is 250 mg/dL. Estimated glomerular filtration rate is 70 mL/minute/1.73 m^2. Using the pooled cohort equation, his calculated ASCVD risk is greater than 20%. He is eager to improve his heart health and to control his risk factors. In addition to antihypertensive and antihyperglycemic therapy, what medications do you recommend to reduce his ASCVD risk?

ANSWER

According to the 2019 ACC/AHA primary prevention guidelines, aspirin may be considered for primary prevention for patients who are at high risk for ASCVD and are not at high bleeding risk. The 2016 ESC guidelines do not recommend aspirin for primary prevention in any patients, including those with DM. Although this patient is certainly at high risk for ASCVD, his key risk factors appear to be modifiable, including hypertension, DM, and hyperlipidemia. His optimal ASCVD—with all his modifiable risk factors optimally managed—is less than 5%. Given the generally poor data with aspirin in primary prevention observed in recent trials with modern background therapies, it is best to focus on management of blood pressure, blood glucose, and blood lipids initially. Once these factors are optimized, it would be reasonable to reassess his ASCVD risk. If it is still elevated and he is still not at a high bleeding risk, aspirin might be considered at that time.

In terms of lipid therapy, because this patient has DM at least a moderate-intensity statin is indicated based on the 2018 AHA/ACC cholesterol guidelines and the 2019 ACC/AHA primary prevention guidelines. He does not have known ASCVD and his LDL is not 190 mg/dL or more. Based on the patient presentation, he does not have any obvious DM-specific risk enhancers or other risk-enhancers, although the duration of his DM is unknown. However, because his ASCVD score is 20% or more based on his current risk factors, he would be recommended to receive high-intensity statin therapy.

In addition, the patient has elevated TG, DM, and at least 1 risk factor (hypertension). However, he should first be optimized on maximally tolerated statin, and a lipid panel should be rechecked in 4–12 weeks. In addition, his TG will likely improve with glycemic control, diet, and exercise. Although he is not indicated for icosapent ethyl at this time, it would be reasonable to reconsider icosapent ethyl at follow-up based on his response to initial therapy.

1. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:e177-232.
2. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e285–350.
3. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315-81.

Table 5. 2019 European Society of Cardiology/European Atherosclerosis Society Guideline Summary for Omega-3 Fatty Acids

Statement	Grade
Statin treatment is recommended as the first drug of choice to reduce cardiovascular disease risk in high-risk patients with hypertriglyceridemia (TG>200 mg/dL)	Class I, Level B
In high-risk (or above) patients with TG 135–499 mg/dL despite statin treatment, O3FA (icosapent ethyl 2 g twice daily) should be considered in combination with a statin	Class IIa, Level B
In primary prevention patients at LDL goal with TG >200 mg/dL, fenofibrate or bezafibrate may be considered in combination with statins	Class IIb, Level B
In high-risk patients at LDL goal with TG >200 mg/dL, fenofibrate or bezafibrate may be considered in combination with statins	Class IIb, Level C
Oral supplementation with highly purified O3FA reduced mortality in MI survivors in one study (GISSI-P) but failed to affect clinical outcomes in subsequent trials using contemporary secondary prevention therapies.	
A recent meta-analysis of available randomized, controlled clinical trials showed no reduction in mortality, MI, or major vascular events associated with O3FA including the subgroup with known coronary artery disease. Therefore, routine treatment with O3FA cannot be recommended.	

GISSI-P = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione; LDL = low-density lipoprotein cholesterol; MI = myocardial infarction; O3FA = omega-3 fatty acid; TG = triglycerides.

Information from: Mach, F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2019;41:111-88.

placebo was not associated with adverse effects on lipid levels and atherosclerotic surrogate markers, contrary to mineral oil (Nicholls 2020).

Several hypotheses have been proposed to explain the reduction in ASCVD events observed in REDUCE-IT, including using high-dose, high-purity EPA and enrolling patients with elevated TG—characteristics shared with the STRENGTH trial. Unfortunately, given the uninspiring results of STRENGTH, these hypotheses now seem less persuasive. Although some researchers have suggested DHA may have counteracted the beneficial effects of EPA in STRENGTH, it seems unlikely that any harmful DHA effects and beneficial EPA effects would be identical in magnitude (Curfman 2020). The two most plausible remaining explanations are that either icosapent ethyl possesses a specific mechanism of benefit that other O3FA products have yet to match or the mineral oil comparator significantly influenced the results. Additional data are needed to definitively answer this question (Curfman 2020).

Guideline Recommendations

The ESC/European Atherosclerosis Society guidelines recommend the addition of icosapent ethyl to statin therapy for high-risk patients with TG 135–499 mg/dL (Table 5). Of importance, the guidelines also recommend against routine use of O3FA in other scenarios (Mach 2020). The 2018 AHA/ACC lipid guidelines do not address O3FA generally or icosapent ethyl specifically (Grundy 2019). In the absence of new data, icosapent ethyl is the preferred O3FA for high-risk patients with elevated TG based on the positive results of the REDUCE-IT trial and the muted results from other trials.

ASPIRIN IN SECONDARY AND PRIMARY PREVENTION OF ASCVD

Primary Prevention

Historic Literature

In contrast to secondary prevention, the recommendation of aspirin for primary prevention of ASCVD has been inconsistent and controversial. Despite being one of the most studied topics in cardiology, a general consensus on the benefits and risks of aspirin for primary prevention has been difficult to achieve, largely because of heterogeneous populations and dosing strategies. Previous guidelines were shaped by two early studies: the Physicians' Health Study and Women's Health Study (Table 6) (Steering Committee of the Physicians' Health Study Research Group 1989; Ridker 2005). The Physicians' Health Study evaluated the use of aspirin 325 mg every other day or placebo in 22,071 healthy male physicians. After a median follow-up of 5 years, the study was terminated early because aspirin demonstrated a 44% RR reduction in the incidence of MI (1.26% vs. 2.17%) (Steering Committee of the Physicians' Health Study Research Group 1989). The Women's Health Study randomized 39,876 healthy women to aspirin 100 mg every other day or placebo. After a median follow-up of 10 years, aspirin demonstrated a 17% RR reduction in the incidence of stroke (RR 0.83; 95% CI, 0.69–0.99) (Ridker 2005).

Table 6. Studies on Aspirin in Primary Prevention Before 2005

Study (Year)	Participants (n)	Trial Design	Aspirin Dose	Baseline Characteristics	Follow-Up (yr)	Key Findings: RR (95% CI)
BDT (1988)	5139	RCT	500 mg/day	53% age >60 yr 100% men 75% former or current smokers Statin use: NR	6	MI: 0.96 (0.73–1.24) Stroke: 1.16 (0.75–1.50) CV death 0.93 (0.72–1.22) Extracranial bleeding 1.42 (0.60–3.36)
PHS (1989)	22,071	RCT	325 mg every other day	Age 53 yr 100% men 50% former or current smokers Statin use: NR	5	MI: 0.56 (0.45–0.70) Stroke: 1.22 (0.93–1.60) CV death: 0.96 (0.60–1.54) Bleeding: 1.32 (1.25–1.40)
ETDRS (1992)	3711	RCT	650 mg/day	52% >50 yr 56% men 100% diabetes 44% hypertension 49% CV disease history Statin use: NR	5	MI: 0.85 (0.73–0.99) Stroke: 1.18 (0.88–1.58) CV death: 0.89 (0.76–1.04)
TPT (1998)	5499	RCT	75 mg/day	Age 57 yr 100% men 41% smokers Statin use: NR	6.8	IHD: 0.81 (0.66–0.99) Stroke: 0.98 (0.66–1.46) CV death: 1.05 (, 0.88–1.26) Major bleeding: 2.00 (0.60–6.62)
HOT (1998)	18,790	RCT	75 mg/day	Age 62 yr 53% men 100% hypertension 16% smokers	3.8	MI: 0.64 (0.49–0.85) Stroke: 0.98 (0.78–1.24) CV death: 0.95 (0.75–1.20) Major bleeding: 1.74 (1.32–2.30)
PPP (2001)	4495	RCT	100 mg/day	Age 64 yr 58% women 68% hypertension 40% hyperlipidemia 17% diabetes 16% lipid-lowering therapy	3.6	MI: 0.69 (0.38–1.23) Stroke: 0.67 (0.36–1.27) CV death: 0.56 (0.31–0.99) Major bleeding: 4.08 (1.67–9.96)
WHS (2005)	39,876	RCT	100 mg every other day	Age 55 yr 100% women 26% hypertension 13% active smokers 54% post-menopausal Statin use: NR	10.1	MI: 1.02 (0.84–1.25) Stroke: 0.83 (0.69–0.99) CV death: 0.95 (0.74–1.22) GI bleeding: 1.22 (1.10–1.34)

BDT = British Doctors' Trial; CV = cardiovascular; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment; IHD = ischemic heart disease; MI = myocardial infarction; NR = not reported; PHS = Physicians' Health Study; PPP = Primary Prevention Project; RCT = randomized controlled trial; TPT = Thrombosis Prevention Trial; WHS = Womens' Health Study.

On the basis of the results of the Physicians' Health Study and Women's Health Study, governing clinical bodies adopted the recommendation of aspirin for primary prevention to reduce the incidence of MI in men and stroke in women (Figure 1). The 2009 United States Preventive Services Task Force recommended the use of aspirin for men age 45–79 years and women age 55–79 years when the potential benefit of aspirin outweighed the potential harm of an increase in GI hemorrhage, as an evidence grade A recommendation (Table 7) (US Preventive Services Task Force 2009).

However, controversy still existed as the 2009 Antithrombotic Trialists' Coalition conducted a meta-analysis of the six

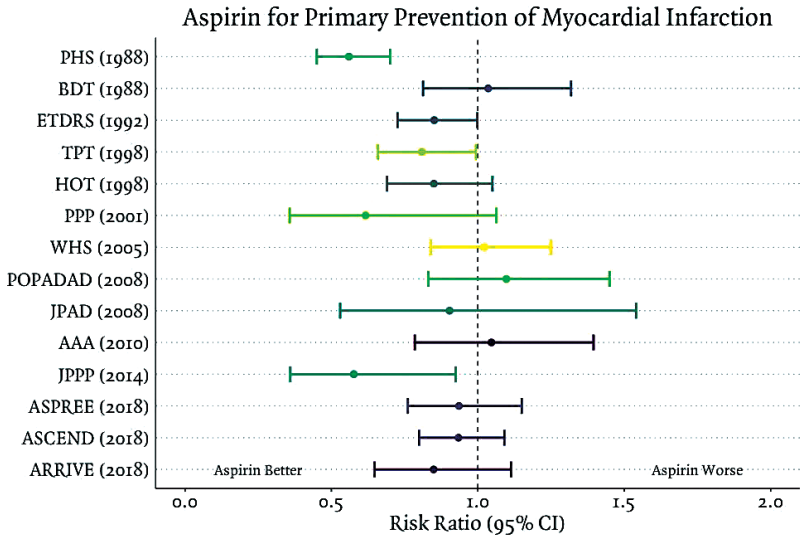

Figure 1. Effect of aspirin for the primary prevention of myocardial infarction in large randomized controlled clinical trials.

major primary prevention trials totaling 95,000 individuals. Aspirin was found to provide a 12% RR reduction in the incidence of serious vascular events (0.51% vs. 0.57% per year) but provided a 42% RR increase in major GI and extracranial bleeds (0.1% vs. 0.07% per year) as shown in Figure 2 (Antithrombotic Trialists' [ATT] Collaboration 2009). Ultimately, the authors concluded that aspirin provides an uncertain net value. Given the persistent uncertainty of the net clinical benefit of aspirin, three large randomized controlled trials were crafted to provide further insight.

Recent Literature

ASCEND

The three trials were designed to evaluate the use of aspirin in three specific populations: type 2 DM, moderate- to high-risk patients, and older adult patients. The ASCEND trial was tasked with identifying the benefit of aspirin 100 mg/day versus placebo in patients with type 2 DM without CVD (ASCEND Study Collaborative Group 2018a). In total, 15,480 patients were followed for an average of 7.4 years. The average patient was a 63-year-old white man with type 2 DM, at moderate risk for ASCVD, and on statin therapy. Treatment with aspirin was found to reduce the RR of vascular events by 12% (RR 0.88; 95% CI, 0.79–0.97; p=0.01) but increased the risk of major bleeding by 29% (RR 1.29; 95% CI, 1.09–1.52 p=0.03). The net clinical benefit of aspirin versus placebo was not significantly different among patients of low-, moderate-, and high-risk for vascular events. Ultimately, the investigators concluded that the magnitude of benefit was counterbalanced by a similar increase in bleeding events in the setting of modern statin use and modern antihyperglycemic agents (ASCEND Study Collaborative Group 2018a).

ARRIVE

In contrast to ASCEND, the ARRIVE investigators sought to determine the risks and benefits of aspirin in patients at moderate CV risk without DM (Gaziano 2018). Eligible patients included men 55 years and older with 2 to 4 risk factors and women 60 years and older with 3 or more risk factors. Risk factors included hyperlipidemia, defined as TC greater than 200 mg/dL for men or greater than 240 mg/dL for women or LDL greater than 130 mg/dL for men or greater than 160 mg/dL for women; active smokers; HDL less than 40 mg/dL; and hypertension, defined as systolic blood pressure greater than 140 mm Hg without antihypertensive therapy, current antihypertensive therapy, or a positive family history of CVD. To estimate risk, investigators conducted a risk factor sensitivity analysis to create inclusion criteria for a moderate-risk population. The PROCAM, Framingham, and SCORE calculators were then used to estimate risk of CHD, stroke, and CV death. A total of 12,546 patients were randomized to aspirin 100 mg/day or placebo and followed for a mean of 5 years (Gaziano 2018). The average patient was a 64-year-old Caucasian man with hyperlipidemia. Slightly less than 50% of patients (43%) were taking statins at baseline. After a 5-year follow-up, no significant difference was observed in the first occurrence of CV death, MI, unstable angina, stroke, or transient ischemic attack (HR 0.96; 95% CI, 0.81–1.13). Notably, the event rate was substantially lower than anticipated compared with the predicted 10-year incidence from the risk calculator. At an average of 5 years of follow-up, the event rate was 4.29% in the aspirin group and 4.48% in the placebo group, despite a baseline ACC/AHA 10-year ASCVD risk score of 17.3% and 17.4% in each group, respectively. Although most bleeding

Table 7. Evolution of United States Aspirin for Primary Prevention of Cardiovascular Disease Guidelines

Organization	Year	Population Age and Risk Factors	Recommendation	Evidence Grade
USPSTF	1996	Asymptomatic adults	Does not recommend for or against use	C
USPSTF	2002	Adults at increased risk for CHD	Recommends clinicians discuss benefits and risks in adult patients at risk of CHD	A
USPSTF	2009	Men 45–79 yr	Recommends use of aspirin to reduce myocardial infarction when benefit outweighs risk	A
		Women 55–79 yr	Recommends use of aspirin to reduce stroke when benefit outweighs risk	A
		Men <45 yr; women <55 yr	Recommends against use	D
		Adults >80 yr	Current evidence is insufficient	I
USPSTF	2016	Adults 50–59 with 10-yr CVD risk ≥ 10%	Recommends use for those not at risk of increased bleeding with life expectancy of >10 yr	B
		Adults 60–69 with 10-yr CVD risk ≥ 10%	Decision should be individualized and balance risk of bleeding against potential benefit	C
		Adults >70 yr	Current evidence is insufficient	I
		Adults <50 yr	Current evidence is insufficient	I
ACC/AHA	2019	Adults 40–70 yr	Aspirin may be considered in those at high ASCVD risk but not high bleeding risk	IIB-A
		Adults >70 yr	Should not be administered on a routine basis	III-C
		Adults at increased risk of bleeding	Should not be administered for primary prevention	III-C

ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular = CHD = coronary heart disease; USPSTF = US Preventative Services Task Force.

Information from: Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:e177-232; Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2016;164:836-45; U.S. Preventative Services Task Force Guide to Clinical Preventive Services, 2nd ed.: report of the U.S. Preventive Services Task Force. Baltimore, MD: Williams & Wilkins, 1996; U.S. Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. Ann Intern Med 2002;136:157-60; U.S. Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009;150:396-404.

was considered mild, a conventionally significant increase was noted in the incidence of GI bleeding in patients receiving aspirin (0.97% vs. 0.46%; HR 2.11; 95% CI, 1.36–3.28) (Gaziano 2018).

ASPREE

Information on the net clinical benefit of aspirin for primary prevention in the older adults has been lacking historically. The ASPREE investigators randomized 19,114 otherwise healthy adults older than 70 years to aspirin 100 mg/day or placebo (McNeil 2018c). The average participant was a 74-year-old white woman with hypertension and hyperlipidemia. After a median follow-up of 4.7 years, the primary end point of death, dementia, or physical disability occurred in 9.7% of patients in the aspirin group compared with 9.5% in the placebo group (HR 1.01; 95% CI, 0.92–1.11) (McNeil 2018c). Notably, a slight increase in all-cause mortality was observed in the aspirin group (5.9% vs. 5.2%, HR 1.14; 95% CI, 1.01–1.29) (McNeil 2018a). No clinically significant difference was noted in the incidence of major adverse CV events (HR 0.89; 95% CI, 0.77–1.03). In contrast, a 38% increase was observed in the risk of major hemorrhage (HR 1.38; 95% CI, 1.18–1.62) largely driven by increased upper GI bleeds (McNeil 2018b).

Guideline Conclusions and Updates

On the basis of ASCEND, ARRIVE, and ASPREE, ACC/AHA updated their recommendations on the use of aspirin for

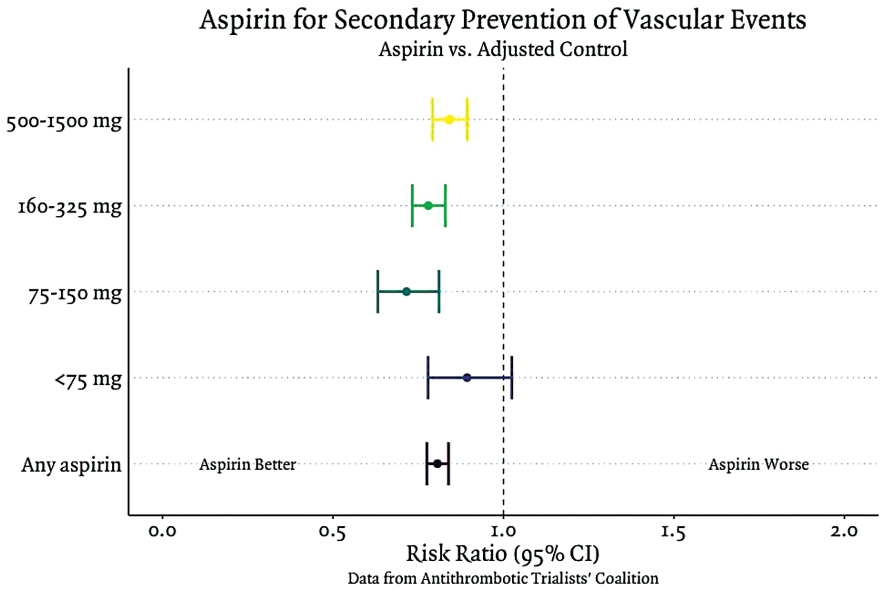

Figure 2. Effect of daily aspirin dose on the secondary prevention of vascular events from the Antiplatelet Trialists' Collaboration meta-analysis.

Information from: Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ 1994; 308:81-106.

primary prevention with their 2019 guidelines (Arnett 2019). First, the committee relaxed the recommendation for use of aspirin in adults younger than 70 years, suggesting that aspirin may be considered for patients at high risk for CVD without an increased risk of bleeding. Second, for adults older than 70 years, aspirin should not be routinely used for primary prevention given the findings of the ASPREE trial. Lastly, bleeding risk should be evaluated in all patients being considered for aspirin, and routine aspirin use should be avoided in those at an increased bleeding risk (Arnett 2019).

Future investigation is still needed to evaluate how clinicians can better estimate CV risk. Routine use of statins, better management of relevant comorbidities such as type 2 DM, and a more robust understanding of ASCVD have all changed how CV risk is estimated. Analysis of participants in the Multi-Ethnic Study of Atherosclerosis (MESA) has suggested that coronary artery calcium scoring may be a useful tool for identifying patients who may benefit from aspirin (Cainzos-Achirica 2020; Miedema 2014).

Based on ACC/AHA guidelines (and using an ASCVD risk score greater than 20% to determine high risk), the MESA investigators found that only 5% of patients would qualify for aspirin use (Cainzos-Achirica 2020). However, based on present data, it is difficult to recommend the routine use of aspirin for primary prevention.

Secondary Prevention

Often mentioned in parallel with statins, the role of aspirin in the secondary prevention of CVD is well-established. The benefit of aspirin in the acute management of CVD was first demonstrated in ISIS-2 (the second International Study of Infarct Survival) when 17,187 patients with a suspected acute MI were randomized in a 2 2 factorial fashion to streptokinase or matching placebo and aspirin or matching placebo. Patients randomized to 1 month of aspirin 162 mg/day demonstrated a 2.6% absolute reduction in death at 35 days compared with placebo (Baigent 1998). To further evaluate the use of aspirin beyond 35 days, a meta-analysis was conducted to determine the benefit of long-term antiplatelet therapy on vascular events in different categories of patients (Collaborative overview [no authors] 1994). The investigators identified 11 trials evaluating the prolonged benefit of antiplatelet therapy (primarily aspirin) in almost 20,000 patients with a history of MI. At 2 years, prolonged antiplatelet therapy reduced the incidence of MI, stroke, or vascular death by 3.3% (Collaborative overview [no authors] 1994). The benefit of aspirin in secondary prevention was further cemented by a 2002 meta-analysis of 195 trials evaluating the use of antiplatelet therapy for secondary prevention of vascular events and primary prevention in high-risk groups. After an average of 2 years of treatment, a 18.7% RR reduction in vascular events was observed (Antithrombotic Trialists' Collaboration

2002). When stratified to aspirin alone, the benefit was found to be consistent and far exceeded the estimated 2-fold increased risk of upper GI bleeding.

Optimal Aspirin Dose in the Setting of Dual Antiplatelet Therapy

Subsequent studies sought to identify the optimal dose of aspirin for prevention of CV events. The CHARISMA trial evaluated the addition of clopidogrel 75 mg/day or placebo to patients with ASCVD or at high risk and receiving aspirin 75–162 mg/day (Bhatt 2006). After a median follow-up of 28 months, no significant difference was observed in the composite primary end point of MI, stroke, or death from CV causes between the clopidogrel plus aspirin and aspirin alone groups (RR 0.93; 95% CI, 0.83–1.05; p=0.22). However, a significantly higher incidence of moderate bleeding was noted in patients receiving clopidogrel and aspirin compared with aspirin alone (2.1% vs. 1.3%; RR 1.62; 95% CI, 1.27–2.08; p <0.001). A post-hoc analysis of CHARISMA grouped patients into three categories: aspirin less than 100 mg/day, aspirin 100 mg/day, and aspirin greater than 100 mg/day (Steinhubl 2009). A total of 15,595 patients had information on aspirin dosing available with 7180 patients receiving less than 100 mg/day, 4961 receiving 100 mg/day, and 3454 receiving greater than 100 mg/day. Patients on higher doses of aspirin were more likely to have a history of vascular disease (84.1% taking more than 100 mg/day vs. 78.0% at 100 mg/day and 76.6% at less than 100 mg/day). A Cox proportional hazards model controlling for potential confounding variables was used to evaluate the effect of aspirin dose on the efficacy and safety outcomes. After adjustment for baseline characteristics, the incidence of the primary composite outcome of death, MI, or stroke was not significantly different among the three groups (9.4% taking less than 100 mg/day, 8.9% at 100 mg/day, and 9.2% at more than 100 mg/day). With respect to the primary safety end point of severe or life-threatening bleeding, unadjusted analysis did not show a clinically significant difference for patients taking aspirin greater than 100 mg/day versus aspirin less than 100 mg/day (HR 1.05; 0.74–1.48). However, a subgroup analysis of patients on clopidogrel revealed a numerically higher—but not conventionally significant—incidence of severe or life-threatening bleeding in patients receiving aspirin more than 100 mg/day (HR 1.12; 0.94–1.33). Given these findings, the investigators concluded that aspirin less than 100 mg/day was equally efficacious as the higher doses without the potential risk of bleeding, particularly when used with an additional antiplatelet agent. More information on the appropriate dose of aspirin for secondary prevention will be available after completion of the ADAPTABLE trial which is evaluating the use of aspirin 325 mg/day versus aspirin 81 mg/day in patients with CHD (Marquis-Gravel 2020). At this time, American College of Chest Physicians, AHA/ACC, and ESC recommend the use of aspirin less than 100 mg/day for secondary prevention of CHD (Smith 2011; Vandvik 2012; Perk 2012).

CONCLUSION

Statins remain the cornerstone of ASCVD secondary prevention, and maximally tolerated doses are recommended for almost all patients with ASCVD independent of LDL. Statins remain an important therapy for primary prevention, especially in patients with DM, LDL 190 mg/dL or higher, or those with ASCVD score 20% or more. Risk-modifiers and patient-centered discussions are key for tailoring therapy for primary prevention. Although commonly used, O3FA supplements have not demonstrated any appreciable impact on ASCVD risk and are not recommended for either the primary or secondary prevention of ASCVD. Icosapent ethyl is the only O3FA to demonstrate clear ASCVD benefit. Icosapent ethyl may be considered in addition to maximally tolerated statin therapy in patients with TG concentrations 150–499 mg/dL and either ASCVD or DM with 2 or more risk factors, although additional data are needed to elucidate its mechanism of benefit. Like statins, aspirin is recommended indefinitely for

Practice Points

- **Both ACC/AHA cholesterol guidelines and primary prevention guidelines were recently updated.**
- **Maximally tolerated statins are recommended for all patients without contraindications and with either ASCVD or LDL 190 mg/dL or higher.**
- **Patients with type 1 or type 2 DM and without ASCVD are indicated for moderate-intensity statins and may be considered for high-intensity statins based on the presence of DM-specific risk-modifiers.**
- **Patients without ASCVD and not meeting the previous criteria should undergo ASCVD risk assessment using the pooled cohort equation. Patients with ASCVD risk 20% or more are indicated for high-intensity statins, whereas those with less than 5% risk should be counseled on maintaining a healthy lifestyle. Patients with an ASCVD risk 5% to less than 7.5% may qualify for moderate-intensity statin based on the presence of risk-enhancing factors. Patients with an ASCVD risk 7.5% to less than 20% are indicated for a moderate-intensity statin and may qualify for a high-intensity statin based on presence of risk-enhancing factors.**
- **Low-dose aspirin is recommended indefinitely for all patients with ASCVD in the absence of contraindications.**
- **Aspirin for the primary prevention of CVD is not recommended for older adult patients, or patients at high-risk of bleeding.**
- **Diabetes mellitus is not an independent indication for aspirin for primary prevention of CVD.**
- **Aspirin for the primary prevention of CVD may be considered in select adult patients (age 40–70 years) who are at high ASCVD risk and who are not at increased bleeding risk.**
- **Omega-3 fatty acids (including over-the-counter supplements) are not routinely recommended for the prevention or treatment of ASCVD in most patients.**
- **Icosapent ethyl 2 g twice daily should be considered in addition to maximally tolerated statin therapy in patients with TG concentrations of 150–499 mg/dL and either ASCVD or DM and several risk factors.**

secondary prevention in all patients without contraindications. However, recent literature and advancements in background therapy have necessitated a reappraisal of aspirin for primary prevention. Aspirin for primary prevention should only be used in patients with very high ASCVD risk who are not at an elevated bleeding risk and in whom other risk factors have been adequately addressed. Aspirin for primary prevention should not be considered a substitute for optimizing blood pressure, lipids, glycemic control, and lifestyle risk factors, such as smoking cessation, diet, and exercise.

REFERENCES

ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563-74.

Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60.

Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86. Published correction appears in BMJ 2002;324:141.

Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:e177-232.

ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018a;379:1529-39.

ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus. N Engl J Med 2018b;379:1540-50.

Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77 917 individuals. JAMA Cardiol 2018;3:225-34.

Baigent C, Collins R, Appleby P, et al. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. BMJ 1998;316:1337-43.

Bays HE, Ballantyne CM, Kastelein JJ, et al. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the multi-center, placebo-controlled, randomized, double-blind, 12-week study with an open-label extension [MARINE] trial). Amer J Cardiol 2011;108:682-90.

Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. Circulation 2019;139:e56-528.

Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706-16.

Bhatt DL, Steg PG, Brinton EA, et al. Rationale and design of REDUCE-IT: reduction of cardiovascular events with icosapent ethyl-intervention trial. Clin Cardiol 2017;40:138-48.

Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11-22.

Budoff MJ, Bhatt DL, Kinninger A et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. Eur Heart J 2020;41:3925-32.

Cainzos-Achirica M, Miedema MD, McEvoy JW, et al. Coronary artery calcium for personalized allocation of aspirin in primary prevention of cardiovascular disease in 2019: the MESA study (multi-ethnic study of atherosclerosis). Circulation 2020;141:1541-53.

Cannon CP, Braunwald E, McCabe CH, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495-504.

Chou R, Dana T, Blazina I, et al. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force. JAMA 2016;316:2008-24.

Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ 1994;308:81-106.

Curfman G. Do omega-3 fatty acids benefit health? JAMA 2020;324:2280-81.

Ganda OP, Bhatt DL, Mason RP, et al. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. J Am Coll Cardiol 2018;72:330-43.

Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 2018;392:1036-46.

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e285-350.

HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med 2014;371:203-12.

Hughes S. 2019. FDA panel recommends high-dose EPA for CV event reduction. Medscape [news alert].

Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. 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 1998;339:1349-57.

Mach, F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111-88.

Manson JE, Cook NR, Lee IM, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. N Engl J Med 2019;380:23-32.

Marquis-Gravel G, Roe MT, Robertson HR, et al. Rationale and design of the aspirin dosing—a patient-centric trial assessing benefits and long-term effectiveness (ADAPTABLE) trial. JAMA Cardiol. 2020;5:598-607.

McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med 2018a;379:1519-28.

McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med 2018b;379:1509-18.

McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. N Engl J Med 2018c;379:1499-508.

Miedema MD, Duprez DA, Misialek JR, et al. Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: estimates from the multi-ethnic study of atherosclerosis. Circ Cardiovasc Qual Outcomes 2014;7:453-60.

Nicholls SJ, Lincoff AM, Bash D, et al. Assessment of omega-3 carboxylic acids in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol: rationale and design of the STRENGTH trial. Clin Cardiol 2018;41:1281-88.

Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. JAMA 2020;324:2268-80.

Perk J, De Backer G, Gohlke H, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012;33:1635-701.

Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). Lancet 1994;344:1383-9.

Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293-304.

Smith SC Jr, Benjamin EJ, Bonow RO, et al., World Heart Federation and the Preventive Cardiovascular Nurses Association. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation 2011;124:2458-73.

Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing physicians' health study. N Engl J Med 1989;321:129-35.

Steinhubl SR, Bhatt DL, Brennan DM, et al. Aspirin to prevent cardiovascular disease: the association of aspirin dose and clopidogrel with thrombosis and bleeding. Ann Intern Med 2009;150:379-86.

Stone NJ, Robinson JG, Lichtenstein AH, et al., American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S1-45.

Toth PP, Philip S, Hull M, et al. Association of elevated triglycerides with increased cardiovascular risk and direct costs in statin-treated patients. Mayo Clin Proc 2019;94:1670-80.

Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e637S-68S.

Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2021-31.

Self-Assessment Questions

1. A 35-year-old African American man with obesity (BMI 32 kg/m^2) has a medical history of heterozygous familial hypercholesterolemia and gout. He denies smoking. Relevant vital signs include blood pressure 128/75 mm Hg and heart rate 80 beats/minute. Relevant laboratory values include A1C 5.8%, TC 280 mg/dL, HDL 45 mg/dL, LDL 210 mg/dL, TG 125 mg/dL. His estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk score is less than 5% using the pooled cohort equation. He is referred to your ASCVD risk reduction clinic for consideration of lipid-lowering therapy. According to the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) primary prevention guidelines, which one of the following is best to recommend for this patient?

   A. No lipid-lowering therapy
   B. Atorvastatin 10 mg daily
   C. Atorvastatin 80 mg daily
   D. Omega-3 fatty acid (O3FA) 1 g daily

2. A 60-year-old woman of South Asian ancestry has a family history that includes her father dying of a myocardial infarction (MI) at age 52 and her mother dying at age 80 of a stroke. The patient's medical history includes hypertension, lupus, and premature menopause. Her vital signs include blood pressure 137/84 mm Hg and heart rate 72 beats/minute. Her current medications are amlodipine 10 mg daily, hydrochlorothiazide 25 mg daily, and hydroxychloroquine 200 mg twice daily. Her most recent lipid panel includes TC 170 mg/dL, HDL 38 mg/dL, LDL 110 mg/dL, and TG 110 mg/dL. Her estimated 10-year ASCVD risk score is 6.9% using the pooled cohort equation. According to the 2019 ACC/AHA primary prevention guidelines, which one of the following is best to recommend for optimizing this patient's ASCVD risk reduction after having a patient-centered risk discussion?

   A. Rosuvastatin 40 mg daily
   B. Pravastatin 40 mg daily
   C. Lovastatin 10 mg daily
   D. Healthy lifestyle to reduce risk factors

3. A 21-year-old white man (BMI is 23 kg/m^2) has no significant medical history other than active cigarette smoking. His family history is negative for premature ASCVD. His blood pressure is 120/80 mm Hg and heart rate is 75 beats/minute. His most recent lipid panel includes TC 150 mg/dL, HDL 48 mg/dL, LDL 80 mg/dL, and TG 110 mg/dL. His estimated lifetime ASCVD risk is 50% using the pooled cohort equation. According to the 2019 ACC/AHA primary prevention guidelines, which one of the following is best to recommend for optimizing this patient's ASCVD risk reduction?

   A. Healthy lifestyle including smoking cessation
   B. Rosuvastatin 10 mg daily
   C. Atorvastatin 80 mg daily
   D. Icosapent ethyl 2 g twice daily

4. A 55-year-old man with recently diagnosed DM has laboratory values that include A1C 8.5%, LDL 95 mg/dL, and TG 220 mg/dL. He has no known history of ASCVD or microvascular disease and no family history of ASCVD. His ASCVD risk score is 12% using the pooled cohort equation. His current medications include dapagliflozin 10 mg daily, enalapril 5 mg twice daily, and metformin 1000 mg twice daily. His cardiologist asks how to optimize his ASCVD risk reduction. Which one of the following is best to recommend initiating for this patient?

   A. Fenofibrate 145 mg daily
   B. Icosapent ethyl 2 g twice daily
   C. O3FA supplement 1 g daily
   D. Atorvastatin 10 mg daily

5. A 68-year-old man has a medical history of three MIs, hypertension, and peripheral arterial disease. His most recent percutaneous coronary intervention was 1 month ago. His medications include aspirin 81 mg daily, ticagrelor 90 mg twice daily, atorvastatin 80 mg daily, and metoprolol tartrate 25 mg twice daily, all taken orally. His blood pressure is at goal. His most recent lipid panel includes LDL 49 mg/dL and TG 175 mg/dL. Which one of the following is best to recommend to reduce this patient's risk of future ASCVD events?

   A. Icosapent ethyl 2 g twice daily
   B. Ezetimibe 10 mg daily
   C. Alirocumab 75 mg subcutaneously every 14 days
   D. No lipid-lowering therapy

6. A 67-year-old woman has a medical history of DM (diagnosed 15 years ago), hypertension, albuminuria, and chronic kidney disease. She continues smoking 1 pack-per-day. Relevant values include blood pressure 120/80 mm Hg, A1C 7%, LDL 65 mg/dL, TG 170 mg/dL, and CrCl 45 mL/min. Current medications include amlodipine 10 mg daily, dapagliflozin 10 mg daily, metformin 1000 mg twice daily, ramipril 10 mg daily, and rosuvastatin 40 mg daily. In addition to smoking cessation, which one of the following is best to recommend to reduce this patient's risk of future ASCVD events?

   A. Initiate ezetimibe 10 mg daily
   B. Initiate aspirin 81 mg daily
   C. Initiate icosapent ethyl 2 g twice daily
   D. Decrease rosuvastatin to 10 mg daily

7. A 40-year-old white man has a medical history of asthma. His ASCVD risk score is 5%. His BMI is 22 kg/m^2. Blood pressure is 110/70 mm Hg. Relevant laboratory values include A1C 4.9%, LDL 125 mg/dL, TG 151 mg/dL. His father died of MI at age 45 and his paternal uncle died of MI at age 42 years old. He is very concerned about ASCVD and wants to do whatever he can to reduce his risk. According to the 2019 ACC/AHA primary prevention guidelines, which one of the following—in addition to encouraging a healthy lifestyle—is best to recommend initiating to optimize this patient's ASCVD risk reduction?

   A. Rosuvastatin 10 mg daily
   B. Icosapent ethyl 2 g twice daily
   C. Aspirin 81 mg daily
   D. O3FA supplement 1 g daily

8. A 30-year-old woman has a medical history of hypothyroidism with no pertinent family history. Her blood pressure is at goal and a routine lipid panel included LDL 110 mg/dL and TG 130 mg/dL. Current medications include levothyroxine 25 mcg daily and a multivitamin daily. According to the ACC/AHA guidelines, which one of the following is best to recommend to minimize this patient's lifetime ASCVD risk?

   A. Atorvastatin 10 mg daily
   B. Aspirin 81 mg daily
   C. O3FA supplement 1 g daily
   D. Encourage healthy lifestyle

9. A 62-year-old man with a medical history of type 2 DM and hypothyroidism who presents with unstable angina. Relevant laboratory values include A1C 6.7%, TC 163 mg/dL, HDL 33 mg/dL, LDL 109 mg/dL, and TG 105 mg/dL. His current medications include aspirin 81 mg daily, ticagrelor 90 mg twice daily, metformin 500 mg twice daily, and levothyroxine 50 mcg daily. Which one of the following is best to recommend initiating to reduce this patient's risk for future atherosclerotic vascular disease?

   A. Evolocumab 140 mg subcutaneously every 2 weeks
   B. Atorvastatin 80 mg daily
   C. Icosapent ethyl 2 g twice daily
   D. Rosuvastatin 10 mg daily

10. A 77-year-old man has a medical history of squamous cell carcinoma, coronary artery disease status post-coronary artery bypass graft 7 years ago, hypertension, type 2 DM, and peripheral arterial disease status post left femoral-popliteal bypass. He presents to clinic today in good spirits. Blood pressure is 127/74 mm Hg. Relevant labs include A1C 7.1%, TC 234 mg/dL, HDL 43 mg/dL, LDL 141 mg/dL, non-HDL 191 mg/dL, and TG 249 mg/dL. Current medications include aspirin 81 mg daily, atorvastatin 10 mg daily, ezetimibe 10 mg daily, hydrochlorothiazide 25 mg daily, metformin 500 mg twice daily. Which one of the following is best to recommend for this patient?

    A. Increase atorvastatin to 80 mg daily.
    B. Initiate fenofibrate 145 mg daily.
    C. Encourage low-fat diet.
    D. Initiate icosapent ethyl 2 g twice daily.

11. A 76-year-old woman with a history of osteoarthritis, moderate aortic stenosis, heart failure with preserved ejection fraction, and hypertension presents to clinic to establish care. Her current medications include: acetaminophen 1000 mg every 8 hours, amlodipine 5 mg daily, hydrochlorothiazide 25 mg daily, spironolactone 25 mg daily, pravastatin 40 mg daily, and aspirin 81 mg daily. Blood pressure is 136/76 mm Hg. Relevant labs include TC 137 mg/dL, HDL 41 mg/dL, LDL 79 mg/dL, and TG 84 mg/dL. Which one of the following would have the largest net-clinical benefit for this patient?

    A. Change pravastatin 40 mg daily to atorvastatin 80 mg daily.
    B. Initiate ezetimibe 10 mg daily.
    C. Initiate O3FA 1 g daily.
    D. Discontinue aspirin 81 mg daily.

12. A 57-year-old woman with a medical history of bone spurs, bipolar disorder type I, hypertension, active smoker, and a pulmonary embolism 2 months ago presents for routine follow-up. Her family history is significant for her mother having a transient ischemic attack at age 48. Blood pressure is 141/79 mm Hg. Relevant labs include TC 173 mg/dL, HDL 42 mg/dL, and LDL 110 mg/dL. Her 10-year ASCVD risk is 11.8%. The patient's current drugs include apixaban 5 mg twice daily, aripiprazole 10 mg daily, chlorthalidone 25 mg daily, and lisinopril 5 mg daily. She was told by her psychiatrist that one of her medications can increase her risk of metabolic disease so she is motivated to reduce her ASCVD risk. Following risk discussion, which one of the following is best to recommend for this patient?

    A. Aspirin 81 mg daily
    B. Ezetimibe 10 mg daily
    C. Rosuvastatin 10 mg daily
    D. No intervention

13. A 79-year-old man with no significant medical history presents with a non-ST segment elevation MI and received one drug-eluting stent. He was loaded with clopidogrel 600 mg once during the percutaneous coronary intervention. The following morning, the team is planning on discharging the patient home. Blood pressure is 123/71 mm Hg. Relevant labs include A1C 5.9%, TC 131 mg/dL, HDL 38 mg/dL, LDL 74 mg/dL, TG 94 mg/dL, and thyroid-stimulating hormone 2.23 mU/L. In addition

to clopidogrel 75 mg daily, which one of the following is best to recommend for this patient??

A. Aspirin 325 mg daily and atorvastatin 80 mg daily
B. Aspirin 81 mg daily and ezetimibe 10 mg daily
C. Aspirin 325 mg daily and evolocumab 420 mg every 4 weeks
D. Aspirin 81 mg daily and rosuvastatin 10 mg daily

14. A 54-year-old woman with a history of multiple transient ischemic attacks, anxiety, and fibromyalgia presents to clinic for routine follow-up. Blood pressure is 122/74 mm Hg. Her pertinent labs include TC 161 mg/dL, HDL 45 mg/dL, LDL 85 mg/dL, and TG 155 mg/dL. Her current medications include aspirin 81 mg daily, citalopram 20 mg daily, and pregabalin 150 mg three times daily. Which one of the following is best to recommend for this patient?

A. Initiate icosapent ethyl 2 g twice daily.
B. Initiate at evolocumab 420 mg daily.
C. Increase aspirin to 325 mg daily.
D. Initiate rosuvastatin 20 mg daily.

15. A 63-year-old man with history of type 2 DM, MI about 10 years ago, heart failure with preserved ejection fraction, and non-sustained ventricular tachycardia presents to establish care with a new cardiology office. Blood pressure is 121/68 mm Hg. His pertinent labs include A1C 6.6%, TC 113 mg/dL, HDL 39 mg/dL, LDL 60 mg/dL, and TG 70 mg/dL. His current medications include aspirin 81 mg daily, losartan 25 mg daily, magnesium oxide 800 mg daily, metoprolol tartrate 25 mg twice daily, multivitamin daily. Which one of the following is best to recommend for this patient?

A. Initiate atorvastatin 40 mg daily.
B. Increase aspirin to 325 mg daily.
C. Discontinue aspirin 81 mg daily.
D. Initiate ezetimibe 10 mg daily.